A RANDOMIZED OPEN LABEL COMPARATIVE CLINICAL STUDY OF SYNBIOTIC AGAINST PROBIOTIC IN THE TREATMENT OF ACUTE DIARRHOEA IN CHILDREN

Dissertation submitted to

THE TAMILNADU

DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment for the award of the degree of

DOCTOR OF MEDICINE

IN

PHARMACOLOGY

INSTITUTE OF PHARMACOLOGY

MADRAS MEDICAL COLLEGE

CHENNAI - 600 003

OCTOBER 2015

CERTIFICATE

This is to certify that the dissertation entitled, **"A RANDOMIZED OPEN LABEL COMPARATIVE CLINICAL STUDY SYNBIOTIC AGAINST PROBIOTIC IN THE TREATMENT OF ACUTE DIARRHOEA IN CHILDREN"** submitted by Dr.S.A.AYISHA, in partial fulfillment for the award of the degree of Doctor of Medicine in Pharmacology by The Tamilnadu Dr.M.G.R.Medical University, Chennai is a Bonafide record of the work done by her in the Institute of Pharmacology, Madras Medical College during the academic year 2012-15.

DEAN

Madras Medical College &

Rajiv Gandhi Govt. General Hospital

Chennai – 600 003.

DIRECTOR AND PROFESSOR,

Institute of Pharmacology,

Madras Medical College,

Chennai – 600 003.

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Place:

Date:

Dr.K.M.Sudha M.D.,
Professor of Pharmacology,
Institute of Pharmacology,
Madras Medical College,
Chennai – 600 003.

ACKNOWLEDGEMENT

I am grateful to the Dean, **Dr. Vimala, M.D.,** Madras Medical College and General Hospital, Chennai who initiated this work with permission.

I would like to express my special thanks and deepest gratitude to **Dr.B.Kalaiselvi, M.D.,** Vice Principal and Director Incharge, Institute of Pharmacology, Madras Medical College, Chennai for her remarkable guidance, continuous suggestions and enduring encouragement throughout the study.

I am very thankful to **Dr.R.Nandini, M.D former director**, Institute of Pharmacology, Madras Medical College for carefully reading and commenting on countless revisions of this study.

I record my sincere thanks to **Dr. Nirmala, M.D.,** Head of the Department of Medical Gastroenterology for granting me permission to do this study in the Department of Medical Gastroenterology, Institute of Child Health, Madras Medical College,Chennai.

I wish to express my sincere thanks to **Dr.K.M.Sudha, M.D.,** Professor, Institute of Pharmacology, Madras Medical College for her untiring support. valuable suggestions and consistent notations in my writings. I am grateful to her for enforcing strict validation of my work and her constant support made me to complete my dissertation successfully and more over on time.

I am greatly indebted to **Dr.B.Vasanthi, M.D.,** Professor, Institute of Pharmacology, Madras Medical College for helping me understand and enrich my idea on writing the dissertation.

I would like to acknowledge **Dr.A.C.Yegneshwaran, M.D.,** Tutor in Clinical Pharmacology, for the numerous discussions that helped me improve my knowledge.

I am grateful to Asst.Professors of the Department, **,Dr.K.Vijaya Rani, M.D., Dr.Deepa, M.D.., Dr.G.Chenthamarai M.D., Dr.E.Brindha M.D,** who supported and provided the necessary information during the study.

I also extend my sincere thanks to all other staff members of this Institute for their wholehearted support. Lastly, I owe a great many thanks to all of my friends who helped and supported me in completing the study.

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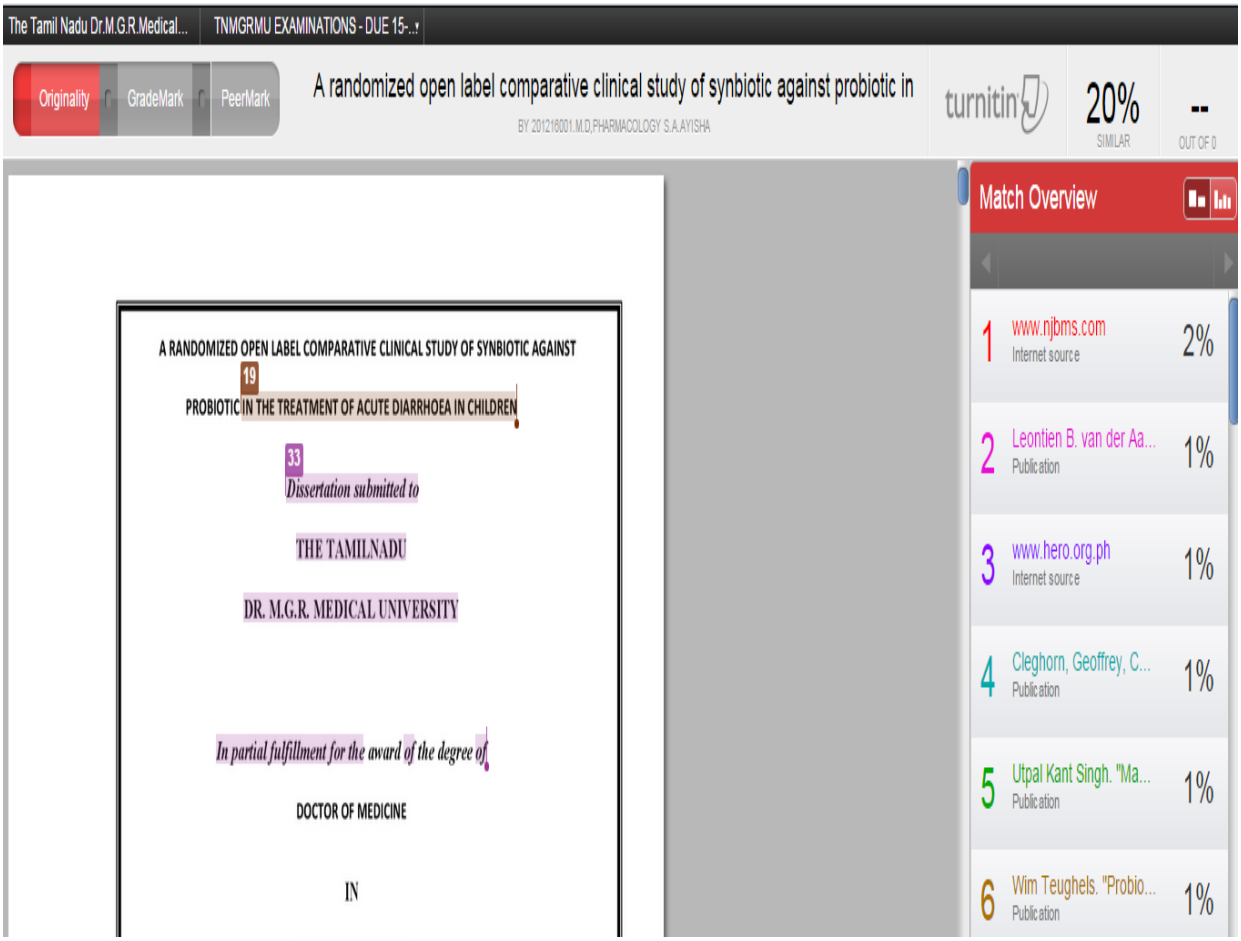

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Randomized open label comparative study of synbiotic versus probiotic in children with acute diarrhea

Dr.S.A.Ayisha, Institute of Pharmacology, Madras Medical College, Chennai

Introduction :

Acute Gastroenteritis is one of the most frequent diseases in the childhood that leads to severe dehydration and has no specific treatment. Probiotics are known to beneficially modulate several host functions, the most important of which are immune responses and intestinal barrier integrity. Lactobacillus is well described as a probiotic which reduces the number of days of hospitalization and also the severity. The overall goal of this study is to compare the efficacy synbiotic against probiotic in reducing the duration and frequency of acute diarrhoea in children..

Materials and methods :

The study was conducted in the Medical Gastroenterology Outpatient department in the Institute of Child Health, Madras Medical College, Chennai between August 2013 to August 2014. 100 children were randomized into 2 groups of 50 each by simple randomization. Group A received standard therapy of Oral Rehydration Salt with Tab.Zinc 20 mg along with synbiotic. Group B received Standard therapy with probiotic. Treatment period was one week and follow-up period one week per patient.

Results :

136 children were screened out of which 100 children were included in the study and all the children completed the study. Clinically Group A (standard therapy with symbiotic) showed statistically significant reduction in the duration and frequency of diarrhea $p<0.001$)

Conclusion: Synbiotic is effective in reducing the duration and frequency of acute diarrhoea in children when administered along with standard therapy.

Keywords : Acute diarrhea, synbiotic, probiotics

Introduction

Diarrhoeal disease is the second most common cause of deaths in children under five years of age (0.58 million or 11%).[1] It is a major cause of childhood mortality and morbidity affecting about 1.7 to 5 billion of children worldwide.[2]

Diarrhoea is defined as a passage of three or more liquid or watery stools in a day.[3] Acute diarrhoea is diarrhoea less than 14 days in duration in a previously normal child usually due to infective etiology. The most common age is 6–24 months**.** In developing countries, children under three years old experience on average three episodes of diarrhoea every year.

Diarrhoea is a major problem in early childhood and environmental conditions like poor sanitation are risk factors. In developing countries, diarrhoea is a leading cause of illness and death in children, creating a tremendous economic strain on healthcare costs.

Diarrhoea is usually a symptom of gastrointestinal infection known as Gastroenteritis, which can be caused by a variety of viral, bacterial, and parasitic organisms. Infection is spread through contaminated food or drinking-water, or from person to person as a result of poor hygiene.

Diarrhoea can cause dehydration and loss of electrolytes. Children, elderly and immunocompromised are at increased risk. Hence, dehydration must be treated promptly to avoid complications like organ damage, shock or coma.

Fluid replacement is the cornerstone of therapy for diarrhoea regardless of etiology. Dehydration is treated with oral rehydration therapy (ORT) when mild or with intravenous fluids when severe. Antibiotics and antimotility agents are not effective in acute diarrhoea. Zinc, a micronutrient at a dose of 20 mg improves absorption of ORS and helps in speedy recovery.[4] The current government of India guidelines recommend low osmolarity ORS, zinc and continued feeding of energy dense foods in addition to breastfeeding in the management of diarrhoea.[5]

Probiotics and synbiotics have been used in the treatment of diarrhoea. Probiotics have been shown to shorten the duration of diarrhoea.[6] Probiotics are microorganisms purported to have a health benefit on the host organism. They can interact with commensal bacteria and can also have a direct impact on the host. Prebiotics are food products defined as nondigestible food ingredients that benefit the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improve host health.

Deviations in composition or function from the usual microbiota, known as dysbiosis, have been observed in certain disease states like Atopy (allergy) and asthma, Coeliac disease, Colon cancer, Type I diabetes, Inflammatory bowel disease (IBD), Irritable bowel syndrome (IBS), GI infections, Antibiotic-associated diarrhoea (AAD) and probiotics and synbiotics have been tried in these conditions.[7]

Probiotics stimulate the mucosal immune mechanisms and beneficially modulate intestinal barrier integrity; Prebiotics increase the numbers of beneficial anaerobic bacteria and decrease the population of potentially pathogenic microorganisms. These phenomena are thought to mediate most beneficial effects, including reduction of the incidence and severity of diarrhoea, which is one of the most widely, recognized uses for probiotics.

Synbiotics are preparations in which probiotic organisms and prebiotics are combined, presumably to form a synergistic relationship. Synbiotics have been proved to reduce markers of intestinal inflammation in disease states and this might change the way in which the immune system recognizes the antigens present in the intestine.

Only few studies regarding the use of probiotics and synbiotics in diarrhoea are available, this study has been undertaken to compare the efficacy of synbiotics with probiotics, when administered along with the standard therapy in reducing the frequency and duration of acute diarrhoea in children.

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Review of Literature

Diarrhoea is defined as a change in the individual bowel habit resulting in more frequent and/or loose stools. It expresses an acute gastrointestinal inflammation (acute gastroenteritis). In childhood, gastrointestinal infection is the most common cause of acute diarrhoea worldwide.[8]

Acute Gastroenteritis is one of the most frequent diseases in the childhood .The median incidence of diarrhoea for all children younger than 5 years of age was 3.2 episodes per child per year. The incidence of diarrhoea was higher in younger children aged 6-11 months, with 4.8 episodes per child per year.[9]

Diarrhoea may be associated with a specific disease of the intestines or secondary to a disease outside the intestines. For instance, bacillary dysentery directly affects the gut, whereas diabetes mellitus causes neuropathic diarrhoeal episodes.

Furthermore, diarrhoea can be considered as acute or chronic disease. Whether acute or chronic, diarrhoea has the same pathophysiologic causes that help identification of specific treatments.

INCIDENCE AND PREVALENCE

The epidemiology of diarrhoea varies in developed versus developing countries.[10] Diarrhoea is a major problem in day care centers and nursing homes, probably because early childhood and environmental conditions are risk factors. Food-borne bacterial infection is a major concern, as several major food poisoning episodes have occurred that were traced to poor sanitary conditions.

Dehydration from GI infections is the second leading cause of morbidity and mortality worldwide, especially in infants and children less than 5 years of age. The median incidence of diarrhoea for all children less than 5 years of age was 3.2 episodes per child per year. The incidence of diarrhoea was higher in younger children, with 4.8 episodes per child per year among children ages 6 to 11 months in comparison with 1.4 episodes per child per year for 4-year-olds. Younger children also had a higher risk for death from acute dehydrating diarrhoea. For children less than 1 year of age and those ages 1 to 4 years, the median mortality rates were 8.5 and 3.8 per 1,000 children per year respectively.[11] Diarrhoea still accounts for 1.6 to 2.5 million deaths annually.

According to the National Center for Health Statistics, 51% of deaths caused by diarrhoeal illness were among patients older than 74 years of age, and 27% were among 55- to 74-year- olds, while 11% were in those younger than 5 years.[12]

Aetiology

The most common cause of diarrhoea is an infection of the intestines due to either a virus, bacteria, or parasite; a condition known as gastroenteritis. These infections are often acquired from food or water that has been contaminated by stool, or directly from another person who is infected.

Viruses are now recognized as the leading cause of diarrhoea in the world, although in many cases an exact pathogen cannot be determined. In industrialized countries the most clinically significant agents in infant acute diarrhoea are viruses mainly group A rotavirus. Other viruses involved are human calicivirus (norovirus and sapovirus, formerly known as

Norwalk and Sapporo virus), astrovirus and enteric adenovirus (types 40 and 41), with some common features.[13]

Most common bacteria are Campylobacter spp. And Salmonella spp., followed by Shigella, Yersinia and Escherichia coli. The major parasitic infections are Giardia, Entamoeba histolytica and Cryptosporidium.

Other causes include food intolerance (lactose), reaction to medications (eg antibiotics), functional bowel disorders like Irritable bowel syndrome, Intestinal disease like Inflammatory Bowel disease, celiac disease.

Pathophysiology

Diarrhoea occurs when the volume of water and electrolytes present in the colon exceeds its capacity for absorption. This can be mainly due to an increase in the secretion and/or a decrease in the absorption level of the small intestine. Decreased intestinal absorption occurs as a result of intestinal damage or inflammation. Viruses causing diarrhoea infect selectively mature enterocytes, causing cell lysis and producing a decrease in disaccharidase activity and in mechanisms for active sodium and water absorption. The consequence is a malabsorptive or osmotic diarrhoea.[14]

Diarrhoea caused by bacterial infection is most frequently secretory. Bacteria can activate one of the intracellular pathways leading to intestinal secretion through enterotoxins.

TYPES OF DIARRHOEA

Based on the duration[15]

1.Acute- less than 2 weeks in duration

2.Persistent- 2-4 weeks duration

3.Chronic- more than 4 weeks duration

Based on the mechanism

1. Secretory diarrhoea

Secretory diarrhoea means that there is an increase in the active secretion, or there is decreased absorption. There is little to no structural damage of the intestinal mucosa. The most common cause of this type of diarrhoea is a cholera toxin that stimulates the secretion of anions, especially chloride ions. Therefore, to maintain a charge balance in the lumen, sodium is carried with it, along with water. In this type of diarrhoea intestinal fluid secretion is isotonic with plasma even during fasting.[16] It continues even when there is no oral food intake.

2. Osmotic diarrhoea

Osmotic diarrhoea occurs when too much water is drawn into the bowels. If a person drinks solutions with excessive sugar or excessive salt, these can draw water from the body into the bowel and cause osmotic diarrhoea. Osmotic diarrhoea can also be the result of maldigestion (e.g., pancreatic disease or Coeliac disease), in which the nutrients are left in the lumen to pull in water. Or it can be caused by osmotic laxatives (which work to alleviate constipation by drawing water into the bowels).

In healthy individuals, too much magnesium or undigested lactose can produce osmotic diarrhoea and distention of the bowel. A person who has lactose intolerance can have difficulty absorbing lactose after an extraordinarily high intake of dairy products.

In persons who have fructose malabsorption, excess fructose intake can also cause diarrhoea. High-fructose foods that also have high glucose content are more absorbable and less likely to cause diarrhoea. Sugar alcohols such as sorbitol (often found in sugar-free foods) are difficult for the body to absorb and, in large amounts, may lead to osmotic diarrhoea. In most of these cases, osmotic diarrhoea stops when offending agent (e.g. milk, sorbitol) is stopped.

3. **Exudative diarrhoea**

Exudative diarrhoea occurs with the presence of blood and pus in the stool. This occurs with inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, and other severe infections such as *E. coli* or other forms of food poisoning.[17]

4. **Inflammatory diarrhoea**

Inflammatory diarrhoea occurs when there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids and a decreased ability to absorb these lost fluids. Features of all three of the other types of diarrhoea can be found in this type of diarrhoea. It can be caused by bacterial infections, viral infections, parasitic infections, or autoimmune problems such as inflammatory bowel diseases. It can also be caused by tuberculosis, colon cancer, and enteritis.

Symptoms of dehydration in children include

1. Dry mouth
2. Dry tongue and lips
3. Sunken eyes
4. Decreased urine output.
5. Irritability
6. Lethargy

Symptoms of severe dehydration in children[18]:

1. Drowsiness
2. Decreased urine output
3. Pale or mottled skin
4. Cold extremities.
5. Rapid and shallow breathing

Signs of severe dehydration

1. Sunken anterior fontanelle
2. Dry mucous membranes
3. Sunken eyes
4. Lack of tears
5. Loss of skin turgor.[19]
6. Delayed capillary refill
7. Reduced muscle mass
8. Peripheral edema

MANAGEMENT OF DIARRHOEA

Acute diarrhoea is usually self-limited[20] Management is generally supportive. As water does not contain electrolytes, drinking water cannot replace the lost electrolytes in diarrhoea. However, the best treatment of acute diarrhoea in a child is the use of oral rehydration solution.[21] WHO recommends zinc along with Oral rehydration therapy for treatment of acute diarrhoea in the developing countries.

Oral Rehydration Therapy (ORT)

ORS replaces the lost fluids and essential salts thus preventing or treating dehydration and reducing the complications. The glucose contained in ORS solution enables the intestine to absorb the fluid and the salts more efficiently. ORT alone is an effective treatment for 90-95% of patients suffering from acute watery diarrhoea, regardless of cause.[22] This makes intravenous drip therapy unnecessary in all but the most severe cases.

The necessary components of glucose based ORT include glucose, sodium, potassium, chloride, and water. Glucose-based ORT takes advantage of glucose coupled sodium transport in the small bowel. Glucose enhances sodium and subsequently water transport across intestinal walls. In children with vomiting and diarrhoea, ORT may be given as 5mL every 2 to 3 minutes in a teaspoon or oral syringe. Nasogastric administration of ORT is an alternative method of administration in a child with persistent vomiting. After starting rehydration therapy, patients should be observed for a reversal of the signs of dehydration, increased stool consistency, and decreased stool frequency.

Maintenance rehydration requires sodium concentrations of 40 to 60 mEq/L, compared to 50 to 90 mEq/L for initial rehydration. ORT solutions with high sodium content may be alternated with water if a low-sodium fluid is not available. The maintenance phase should provide 100 to 150 mL/kg per day plus additional replacement for stool losses.

Clear fluids, such as soda, apple juice should be avoided in both the rehydration and maintenance phase of dehydration. Those solutions are hyperosmolar and may draw free water into the gut lumen and cause hypernatremia. In addition, high glucose concentrations may produce osmotic diarrhoea.

Glucose-based ORT primarily prevents dehydration without much influence on the duration of diarrhoea or stool volume; low-osmolarity ORT solutions (rice- or cereal-based), however, reduce the diarrhoea stool number, volume, and frequency, as well as the duration of diarrhoea, and the replacement volume requirement.

The efficacy of rice-based ORT solutions may be a result, in part, of their hypotonicity, which promotes intestinal water absorption.[23] Also, slow rice hydrolysis allows some rice (glucose) absorption to take place before hydrolysis occurs. Starch and simple proteins provide more cotransport molecules with a lower intraluminal osmotic load, thus increasing fluid and electrolyte uptake by enterocytes and reducing stool losses. Therefore, a larger carbohydrate load can be given with rice solutions, resulting in a greater nutritional advantage.

If ORT does not improve the fluid status and the patient continues to produce frequent, large-volume watery stools, close supervision with medical support is

warranted. Weight loss of 9% to 10% is considered severe and requires IV fluid replacement with Ringer lactate or normal saline.

Intravenous fluid therapy is also indicated in patients with uncontrolled vomiting, the presence of a paralytic ileus, stool output greater than 10 mL/kg per hour, shock, or loss of consciousness. Rapid IV rehydration is preferred over more prolonged deficit-replacement regimens for restoring extracellular fluids and electrolytes because it more effectively reestablishes gastrointestinal and renal perfusion.[24] Early refeeding as tolerated is recommended.

The American Academy of Pediatrics guidelines recommend age-appropriate diet resumption as soon as dehydration is corrected. Breast milk, lactose-free soy formula, and cow's-milk-based formulas often can be continued. Early initiation of feeding has shortened the course of diarrhoea. In a study of severely malnourished children younger than 5 years of age with diarrhoea, using a standardized protocol of slower oral rehydration, immediate feeding, and intensive management of complications resulted in a significant reduction of mortality as compared with standard therapy. Initially, easily digested foods, such as bananas, applesauce, and cereal, may be added.

Foods high in fiber, sodium, and sugar should be avoided. Lactase deficiency may be exacerbated among known lactase-deficient patients and may persist up to 10 days.

ORAL REHYDRATION SOLUTION (ORS) - TYPES

1. GLUCOSE BASED – ORS(Standard WHO ORS) : Total osmolarity of 311 mmol/litre
2. LOW- OSMOLARITY ORS- Total osmolarity of 245 mmol/litre
3. CEREAL BASED ORS- Rice- based ORS
4. ORS WITH OTHER NUTRIENTS (Glycine/Alanine)
5. HOME-MADE ORS

FLUID THERAPY

PLAN A for 'no dehydration'

Provision of normal daily requirement of fluids and

Replacement of ongoing losses to prevent dehydration.

Replacement is done with

1. Home available fluids

- Solution made from Sugar and Salt (Homemade)

  Sugar 40gm + Salt Nacl 4gm in 1 litre of water
- Rice water with Salt (Kanji)
- Lassi with Salt
- Coconut water
- Dhal Water
- Lemon Water.

Fluids not suitable

- Glucose water without Salt.
- Fluids consumed on very small quantities such as tea, coffee.

2. ORS

For children under 2 years, 50-100ml of ORS to be given after each stool. 100-200 ml of ORS for children above 2 yrs

PLAN B for 'Some dehydration'

The Fluid therapy contains 3 components

1) Rehydration therapy – correction of existing water and electrolytes deficit.
2) Maintenance therapy – replacement of ongoing losses.
3) Provision of normal daily requirements of fluids.

Rehydration therapy

Give 75ml/kg of ORS in the first 4 hours.

PLAN C for 'Severe dehydration'

Children with severe dehydration should be given rapid IV rehydration.

The best IV fluid is Ringer lactate (RL) solution. The ideal preparation would be ringer lactate with 5% dextrose. If RL is not available, normal saline 0.9% can be used.

Give 100ml/kg of solution as follows.

In children < 12 months	**In older children**
First 30ml/kg in 1 hour	First 20ml/kg in 30 minutes
Then 70ml/kg in 5 hours	Then 70ml/kg in 2.5 hours

Monitoring:

Reassess the hydration status every 15 minutes until a strong radial pulse is felt and when the full volume of iv fluid is over.

Antimicrobial Therapy

The indiscriminate use of antimicrobial therapy in GI infections produces increase in antimicrobial resistance, side effects of antimicrobial agents, and the threat of superinfections owing to eradication of normal flora. Increasing fluoroquinolone resistance in *Campylobacter* and multidrug resistance in *Salmonella* species worldwide reinforce the importance of judicious use of antibiotics and prudent infection control measures.[25,26] Furthermore, it stresses the need to take local susceptibility patterns into account in the selection of initial choice of antimicrobial regimen.

Antibiotics are not essential in the treatment of most mild diarrhoeas, and empirical therapy for acute GI infections may result in courses of unnecessary antibiotics. However, appropriate antibiotic therapy shortens the duration of illness and reduces morbidity in some bacterial (cholera, enterotoxigenic *E. coli*, shigellosis, campylobacteriosis, yersiniosis) infections and can be lifesaving in invasive infections (*C. difficile*, salmonellosis).

Antibiotic treatment also reduces the duration and shedding of organisms in infections with susceptible *Shigella* species and possibly in infection with susceptible *Campylobacter* species.

It is also important to note that outcomes of some bacterial diarrhoeal illnesses may be worsened by the use of antibiotics. Antibiotic treatment may prolong asymptomatic carriage of *Salmonella.*[27] In patients infected with *E. coli* O157, use of an antimicrobial agent may worsen the risk of hemolytic uremic syndrome (HUS)[28], which is defined by the triad of acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia, by increasing the production of shiga-like toxin.[29]

Antimotility Agents

Antiperistaltic drugs such as diphenoxylate and loperamide[30] offer symptomatic relief in patients with mild diarrhoea. However, these agents are contraindicated in most toxin-mediated diarrhoeal illnesses (enterohemorrhagic *E. coli*, pseudomembranous colitis, shigellosis) and thus should be avoided in patients with high fever and bloody diarrhoea. Slowing of fecal transit time is thought to result in extended toxin-associated damage.

Feeding

Early feeding may decrease the intestinal permeability changes induced by infection, reduce illness duration, and improve nutritional recovery.[31] The recommendations after the period of rehydration are:

• Continuation of breastfeeding in all cases.

• In formula-fed infants continuation of a nondiluted formula, without restriction of lactose intake.

• Resumption of full normal diet in older children, except for avoiding foods rich in simple sugars, due to its osmotic load.

Micronutrients

Zinc has been the main micronutrient implied in the diarrhoeal process. Studies performed in developing countries have shown its effectiveness in the treatment of acute and persistent diarrhoea in children younger than 5 years. This has led the WHO and UNICEF to recommend treatment with zinc in all children with diarrhoea in developing countries.[19]

Probiotics

The addition of probiotics has shown to shorten the duration of the diarrhoea. A moderate clinical benefit of some probiotics has been shown in the treatment of acute watery diarrhoea, mainly by rotavirus in infants and young children.[6] This effect seems to be: moderate in reducing diarrhoea by 17–30 hours; strain dependent with *Lactobacillus GG* most effective; not effective in bacterial invasive diarrhoea; effective when it is administered early in the disease to children in developed countries

Synbiotics

Synbiotics are combination of probiotics and prebiotics. They have been found to be effective in Irritable bowel syndrome, atopy and allergy, eradication of H.pylori, apthous ulcer.[7]

ZINC:

1. Zinc is a micro-nutrient and promotes immunity.
2. It is an important antioxidant and preserves cellular membrane integrity.
3. Promotes the growth and development of the nervous system.
4. Rich sources of Zinc are foods of animal origin, such as meat and fish.
5. Zinc is also present in nuts, seeds, legumes, and whole grain cereal, but the high phytate content of these foods interferes with its absorption.
6. Zinc cannot be stored in the body, and zinc excretion through the gastrointestinal tract is increased during episodes of diarrhoea.[32]

MECHANISM OF ACTION:

- Zinc reduces the fluid and salt loss in stools by improving mucosal permeability.[33]
- Accelerated regeneration of mucosa
- Increased levels of brush-border enzymes
- Enhanced cellular immunity
- Higher levels of secretory antibodies
- Zinc improves absorption of ORS and reduces the severity and duration of illness.[34]
- Reduces need for antibiotics.[35]
- Reduces the chances of complications.
- Full dose for 14 days protects against diarrhoea and pneumonia for next 3 months.
- Acts as a general tonic-improves appetite and promotes growth

FORMULATIONS OF ZINC

1. Zinc sulphate
2. Zinc acetate
3. Zinc gluconate

DOSAGE OF ZINC:

1. Less than 6 months- 10 mg/day
2. More than 6 months- 20mg/day.

DURATION OF TREATMENT: 2 weeks

EFFICACY OF ZINC IN DIARRHOEA:

- 15% faster recovery during the episode of diarrhoea.[36]
- 16 % decrease in duration of diarrhoea.[37]
- 24% decrease in frequency of episodes lasting more than 7 days.
- 9-23% decrease in frequency of stools.[38]
- Up to 31% reduction in stool output during the episode of diarrhoea
- 42% reduction in treatment failure or death in persistent diarrhoea.[39]

SYNBIOTICS AND PROBIOTICS

THE INTESTINAL MICROFLORA

The human intestines host at least 400 different bacterial species.[40] Approximately 55% of faecal mass consists of bacteria. Micro organisms from the mother and the environment colonize the gut of the infants after birth.

Factors like mode of delivery, prematurity, hospitalization, use of antibiotics after birth and type of feeding influence the pattern of implantation of the beneficial microbes.

The intestinal microflora are involved in various nutritional functions, such as breakdown of Indigestible dietary carbohydrates, production of short chain fatty acids (SCFA), synthesis of amino acids and vitamins.

The intestinal micro flora plays a vital role in the development of local immune system.

THE INTESTINAL MICROFLORA AND THE IMMUNE SYSTEM

Gut-associated lymphoid tissue (GALT) is the largest mass of lymphoid tissue found in the gastrointestinal tract.[41] The GALT interacts with intestinal bacteria that are presented by dendritic cells through two types of receptors, Toll-like receptors (TLR) and nucleotiede-binding oligomerization domain (NOD) molecules.

The intestinal microflora appears to be essential for the development of the GALT. Studies have shown that mice without microflora have poorly developed GALT with very few numbers of intestinal intraepithelial lymphocytes , hypoplastic Peyer's patches with less germinal centres and reduced numbers of plasma cells that produces IgA.

SYNBIOTICS

Synbiotics are synergestic combination of probiotics and prebiotics that improves the survival and implantation of beneficial live microorganisms in the gastrointestinal tract of the host.[42]

Prebiotics

Prebiotics are non digestable food ingredients that selectively stimulates the growth and activity of bacterial species already established in the colon.

Commonly used prebiotics are

1. Oligofructose
2. Inulin
3. Galactooligosaccharides
4. Lactulose
5. Breast milk.

Lactulose is a synthetic disaccharide used as a drug for the treatment of constipation and hepatic encephalopathy. The prebiotic oligofructose is found naturally in many foods, such as wheat, onions, bananas, honey, garlic, and leeks. Oligofructose can also be isolated from chicory root or synthesized enzymatically from sucrose.

Fermentation of oligofructose in the colon results in a large number of physiologic effects, including:

- Increasing the numbers of bifidobacteria in the colon
- Increasing calcium absorption

- Increasing fecal weight
- Shortening gastrointestinal transit time
- Possibly, lowering blood lipid levels

The increase in colonic bifidobacteria has been assumed to benefit human health by producing compounds to inhibit potential pathogens, by reducing blood ammonia levels, and by producing vitamins and digestive enzymes.

Any prebiotic should possess the following characteristics:

- alter colonic flora towards healthier composition
- stimulate the growth of beneficial bacteria commensal to the colon, by acting as their substrate selectively
- neither get hydrolyzed nor absorbed in the upper part of GIT
- inducing beneficial effects to the host luminally or systemically.

Among the food ingredients, non digestable carbohydartes (oligo and polysaccharides), some peptides and proteins and certain lipids (both ethers and esters) are candidate prebiotics. Because of their chemical structure, these compounds are not absorbed in the upper part of GIT or hydrolyzed by human digestive enzymes, serving as substrates for the endogenous colonic bacteria, thus indirectly providing the host with energy, metabolic substrates and essential micro nutrients.

Sources of probiotics: [43]

- Soybeans
- Jicama
- Chicory Root
- Raw Oats
- Unrefined Wheat
- Unrefined Barley
- Breast Milk.
- Mutated bacterial species of Clostridim butyricum, Streptococcus fecalis, Bacillus mesentricus

MECHANISM OF ACTION OF PREBIOTICS:

- Enhancing host immunity (IgA production, cytokine modulation, etc.)
- Metabolic effects: production of short-chain fatty acids, fat metabolism, absorption of ions (Ca, Fe, Mg)

Probiotics

Probiotics are live microorganisms administered in adequate amounts with beneficial health effects on the host. Eli Metchinikoff, the Ukranian born Nobel prize winner suggested that the dependence of the intestinal microorganisms on food makes it possible to modify the flora in our bodies and replace the harmful microbes by useful microbes.

To improve the chances of survival in the intestine, a probiotic should be non pathogenic, non toxic and resistant to acidic pH and bile salts.

Probiotics should be able to:

- survive intestinal pH
- adhere to mucosa
- colonize the intestine
- produce antimicrobial substances
- antagonize pathogenic bacteria

Common sources of probiotics:

- Yogurt
- Kefir
- Pickles
- Fermented Kombucha Tea
- Soy Beans
- Dark Chocolate

MECHANISM OF ACTION OF PROBIOTICS:[44]

Immunologic benefits

- Activate local macrophages to increase antigen presentation to B lymphocytes and increase secretory immunoglobulin A (IgA) production both locally and systemically
- Modulate cytokine profiles
- Induce hyporesponsiveness to food antigens

Nonimmunologic benefits

- Digest food and compete for nutrients with pathogens
- Alter local pH to create an unfavorable local environment for pathogens
- Produce bacteriocins to inhibit pathogens
- Scavenge superoxide radicals
- Stimulate epithelial mucin production
- Enhance intestinal barrier function
- Compete for adhesion with pathogens
- Modify pathogen-derived toxins

IMPORTANT STRAINS IN PROBIOTIC FORMULATIONS:

Most important members in the probiotic formulations are

1. Bifidobacteria
2. Lactobacillus.
3. Streptococcus
4. Bacillus
5. Clostridium
6. Streptomyces
7. Yeasts and moulds like Saccharomyces boulardii

Lactobacillus species:

They are gram positive , lactic acid producing bacteria. They are found mainly in the small intestine. *Lactobacillus sporogenes* is non pathogenic bacterium naturally occurring in intestine. It is responsible for synthesis of vitamin B complex and vitamin D and also responsible for synthesis of digestive enzymes. These spores proliferate in the small intestine and produce lactic acid which inhibits the enteric pathogenic organisms. *Lactobacillus rhamnosus* improves body immunity and prevents antibiotic associated diarrhoea .*lacto bacillus reuteri* is used in prevention of H.pylori and gingival infection. *lactobacillus acidophilus* and *Lactobacillus plantarum* are also used as probiotic supplements.

Bifidobacterium species

Bifidobacteria are gram positive , micro aerophillic that are highly prevalent in human intestines. *Bifidobacterium animalis* and *bifidobacterium longum* are used in infantile diarrhoea

Streptococcus faecalis

They are gram positive , aerobic , non spore forming cocci that proliferate with *bacillus mesentricus* and *clostridium butyricum* to produce lactic acid which inhibit harmful bacteria.

Clostridium butyricum

They are live gram positive spore forming bacilli producing butyric acid and acetic acid which decrease intestinal ph and prevents growth of harmful bacteria.

Bacillus species:

Bacillus mesentricus and spores of Bacillus clausii have probiotic action. Live gram positive spore forming bacilli that produces an amylolytic enzyme and protease to activate proliferation of streptococcus.

USES OF PROBIOTICS

GASTROINTESTINAL TRACT:

Probiotics containing β galactosidase helps in improving lactose intolerance. Intake of probiotics like Saccharomyces cerevisiae helps in degradation of sucrose in children with sucrase deficiency . Deficiency of beneficial micro organisms and overgrowth of clostridium difficle are responsible for the occurrence of Antibiotic associated diarrhoea .Use of Saccharomyces boulardii has been shown to improve the condition by replacing the beneficial micro flora.

Probiotics are also being used in prevention and treatment of Rotavirus associated diarrhoea.[45] The effects are due to production of acids, hydrogen peroxide, antimicrobial substances, competition for nutrients or adhesion receptors, antitoxin actions and stimulation of immune system. Probiotics have also been found to be ffctive in antibiotic associated diarrhoea.[46]

Lactobacillus reduces the risk of colorectal cancer by reducing the activity of certain fecal enzymes which convert the procarcinogens to carcinogens.

Eradication of Helicobacter pylori

Several lactobacilli and bifidobacterial strains, as well as *Bacillus clausii*[47] appear to reduce the side effects of antibiotic therapies and improve patient compliance. Several strains were effective in decreasing side effects and increasing the eradication rates.[48]

Hepatic encephalopathy

Prebiotics such as lactulose are commonly used for the prevention and treatment of this complication of cirrhosis.

Irritable bowel syndrome (IBS)

Several studies have demonstrated significant therapeutic gains with probiotics in comparison with placebo. A reduction in abdominal bloating and flatulence as a result of probiotic treatments is a consistent finding in published studies; some strains may ameliorate pain and provide global relief (*B. infantis* 35624) in addition. *Lactobacillus reuteri* improves colicky symptoms within one week.[49]

UROGENITAL INFECTIONS:

L.rhamnosus and L.reuteri strains when applied topically helps in prevention of urogenital infections.

ATOPIC DISEASE:

Lactobacilli reduce the gut permeability, increases gut specific IgA response, promotes the barrier function of the intestines by restoring beneficial microbes to normal level. They also enhance the production of TGF-β and IL-10 and increase the level of cytokines that promote the production of IgE antibodies.

OROPHARYNGEAL INFECTIONS

α-Hemolytic Streptococci have an interfering activity against pathogens that cause otitis media.

EFFECT ON CANDIDIAL INFECTIONS

Probiotics reduce the prevalence of oral candidiasis and risk of hyposalivation in elderly.

APHTHOUS ULCER

Probiotics are beneficial in treatment of recurrent aphthous ulcers of the mouth. The ability of lactobacillus to increase the activity of phagocytes must be the key factor in combating recurrent aphthous ulcer.[50]

HALITOSIS

Probiotics prevent the growth of odour causing organisms and hence used in the treatment and prevention of halitosis.

This study is undertaken to compare the efficacy of synbiotic with probiotic in acute diarrhoea in children.

OBJECTIVE

To evaluate the safety, efficacy and tolerability of synbiotic against probiotic in reducing the episodes (frequency) and the duration of acute diarrhoea.

METHODOLOGY

Study design:

A randomized open label comparative study

Study population:

Children aged 6 months- 5 yrs with acute diarrhoea

Study Center:

Institute of Pharmacology in collaboration with

Out-patient department of Medical Gastroenterology, Institute of Child Health, Madras Medical College, Chennai.

Study period:

August 2013 to August 2014

Study duration: 2 weeks

1 week of treatment + 1 week follow-up per patient.

Sample size:

100 (Group A-50, Group B-50)

Eligibility criteria

Inclusion criteria:

- Age – 6 months- 5 yrs
- Sex - both genders
- Children with acute diarrhoea (less than 14 days duration)
- Parents willing to give written informed consent.

Exclusion criteria

- Children with Persistent diarrhoea
- Children with severe dehydration
- Children with severe malnutrition
- Children having respiratory / systemic infection
- Subject who participated in any investigational drug within 30 days prior to study screening
- Children with known hypersensitivity for synbiotics or probiotics
- Children with chronic systemic illness
- Parents not willing to give written informed consent.

STUDY PROCEDURE:

The study was conducted after obtaining the approval from Institutional Ethics Committee. Parents of children aged 6months to 5 years with acute diarrhoea attending the outpatient department of Medical Gastroenterology, Institute of Child Health, Madras Medical College were explained about the study purpose and procedures.

Written informed consent was obtained from the parents, in the prescribed format in regional language prior to the performance of any study related procedures. If the parent was illiterate, left thumb impression was sought. This was done in the presence of an impartial witness. The demographic details of the patients were obtained and recorded.

Children were screened by complete medical history, clinical examination and laboratory investigations. Subjects who fulfilled the inclusion and exclusion criteria were enrolled in the study and randomized to either Group A or Group B.

RANDOMIZATION:

The enrolled patients were randomized by simple randomization into either group A or B.

TREATMENT PLAN:

GROUP A (n=50):

Standard treatment plus synbiotic 5 ml twice daily for 1 week

GROUP B (n=50):

Standard therapy plus probiotic 5 ml twice daily for 1 week

STANDARD THERAPY

- Oral rehydration therapy
- Tab.Zinc sulphate 20 mg one tablet daily for 2 wks plus

SYNBIOTIC

Composition of Synbiotic: per 5 ml

1. Streptococcus faecalis T-110 - 30 million
2. Clostridium butyricum TO-A- 2 million
3. Bacillus mesentricus TO-A – 1 million
4. Lactobacillus sporogenes- 50 million

Dosage: Dry syrup made upto 50 ml by adding water. 5 ml to be taken orally twice a day.

The constituted solution must be used within five days and the remaining discarded.

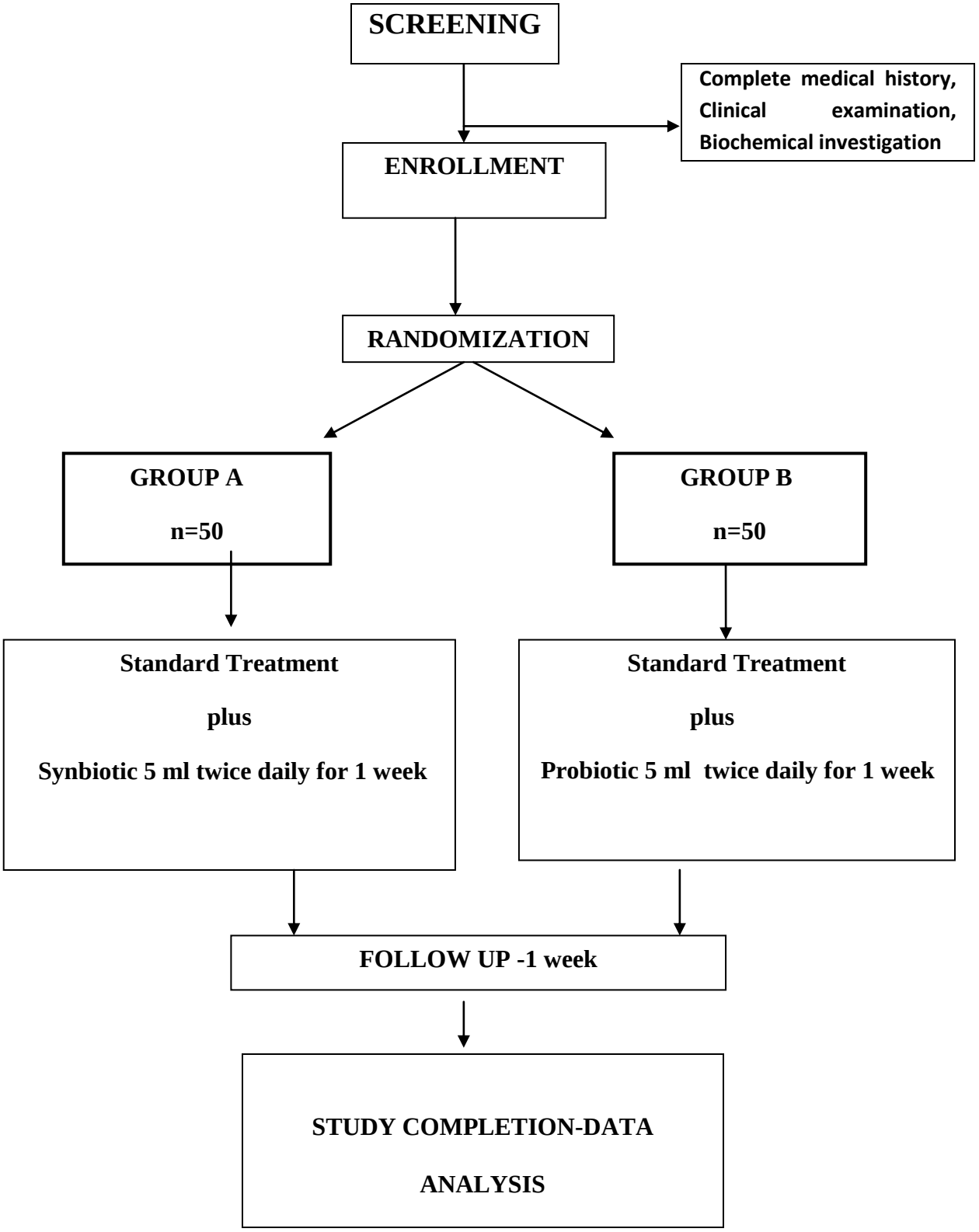
PROBIOTIC

Composition per 5 ml

1. Bacillus clausii- 2 billion spores / vial

   Dosage- One vial twice daily for 1 week. Each vial contains 5 ml. Contents of the vial to be emptied and taken orally.

STUDY FLOW CHART



Visit 1 – Screening and enrollment

- Informed consent obtained
- Demographic details obtained
- Randomization done
- Medical history obtained
- Vital signs recorded
- General & systemic examination done
- Assessment of Diarrhoea done
- Lab Investigations done
- Study medications given for 3 days
- Parents asked to return empty cartons during subsequent visits

Visit 2 (Day 3)

- Empty cartons received and compliance checked
- Vital signs recorded
- General & systemic examination done
- Assessment of Diarrhoea done
- Adverse events if any monitored
- Study medications given for 4 days
- Parents asked to return empty cartons during subsequent visits

Visit 3 (Day 8)

- Empty cartons received and compliance checked
- Vital signs recorded
- General & systemic examination done
- Assessment of Diarrhoea done
- Adverse events if any monitored

Visit 4 (Day 16)

- Vital signs recorded
- General & systemic examination done
- Investigations performed

The following laboratory investigations for Assessment of Diarrhoea were performed in the children at Day 1 and Day 16.

Investigations:

- Haematology
  - Haemoglobin
  - RBC Count
  - Total leucocyte count Differential count
  - Platelet count
- Blood sugar
- Blood Urea
- Serum creatinine
- Serum electrolytes
- Liver function test
  - SGOT
  - SGPT

ASSESSMENT OF DIARRHOEA:

The severity of dehydration- no dehydration, some dehydration, severe dehydration

Diarrhoea- frequency and duration.

Feeding practices

Any concurrent illnesses like Pneumonia, otitis media

ASSESSMENT OF DEHYDRATION

Severe dehydration:

Two of the following signs have to be present

Lethargy or unconsciousness

Sunken eyes

Not able to drink or drinking poorly

Skin pinch goes back very slowly

Some dehydration

Two of the following signs have to be present**:**

Restlessness or irritability

Sunken eyes

Drinks eagerly

Skin pinch goes back slowly

No dehydration

Two of the following signs has to be present**:**

Well, alert child

Eyes normal

Drinks normally, not thirsty

Skin pinch goes back quickly

Recovery & Follow up:

. Recovery is defined as the passage of first semi solid stools or no stools in the previous 18hrs. The findings were recorded in a pre-designed proforma and the parent was asked to bring the child for follow up after 1 week.

Adverse drug effects:

Parents were advised to report as soon as possible in case of any adverse drug reactions (ADR) or occurrence of other illness or consumption of concomitant medications. Any adverse event observed or reported by the parent was recorded.

Causality assessment of adverse drug reactions was done using WHO scale. Severity assessment done by Modified Hartwig Seigel severity assessment scale.

WHO- Causality assessment scale:

Causality term	Assessment criteria
Certain	Event or a laboratory test abnormality with plausible time relationship to drug intake. Cannot be explained by disease or other drugs. Response to withdrawal plausible Event definitive pharmacologically or phenomenologically. Rechallenge satisfactory, if necessary
Probable/likely	Event or a laboratory test abnormality with reasonable time relationship to drug intake Unlikely to be attributed to disease or other drugs Response to withdrawal clinically reasonable Rechallenge not required.
Possible	Event or a laboratory test abnormality with reasonable time relationship to drug intake Cold also be explained by disease or other drugs. Information on drg withdrawal may be lacking or unclear
Unlikely	Event or a laboratory test abnormality with a time to drug intake that makes a relationship improbable Disease or other drugs provide plausible explanations
Conditional / unclassified	Event or a laboratory test abnormality with a time to drug intake that makes a relationship impossible. More data for proper assessment needed

MODIFIED HARTWIG SIEGEL SCALE:

Mild	**Level 1**	No change in treatment required because of ADR.
	Level 2	Drug changed / discontinued No change in treatment required because of ADR, no increase in duration of hospital stay.
Moderate	**Level 3**	Drug changed / discontinued, treatment required but no increase in duration of hospital stay.
	Level 4a	Level 3+ increase in duration of hospital stay by atleast one day.
	Level 4b	ADR is the reason for admission.
Severe	**Level 5**	Level 4 requiring intensive medical care.
	Level 6	ADR causing permanent harm
	Level 7	ADR causing death directly/ indirectly.

STATISTICAL ANALYSIS:

The obtained data was analyzed statistically. Distribution of age was analysed using ANOVA and Sex distribution was analyzed by Chi square test.

The biochemical investigations were performed on Day 1 and Day 16. The difference within the groups before and after treatment were analyzed using student's paired t-test whereas the difference between the Groups A and B were analyzed using One Way ANOVA.

The difference within the groups in diarrhoea were analyzed using student's paired t-test whereas the difference between the groups A and B in Diarrhoea assessement were analyzed using One way ANOVA.

$p < 0.05$ is considered to be statistically significant.

RESULTS

This study was conducted to evaluate the safety, efficacy and tolerability of synbiotic against probiotic in reducing the episodes (frequency) and the duration of acute diarrhoea in children.

136 children were screened, of which 36 were excluded from the study as they had severe dehydration.

All the 100 children completed the study. There were no dropouts.

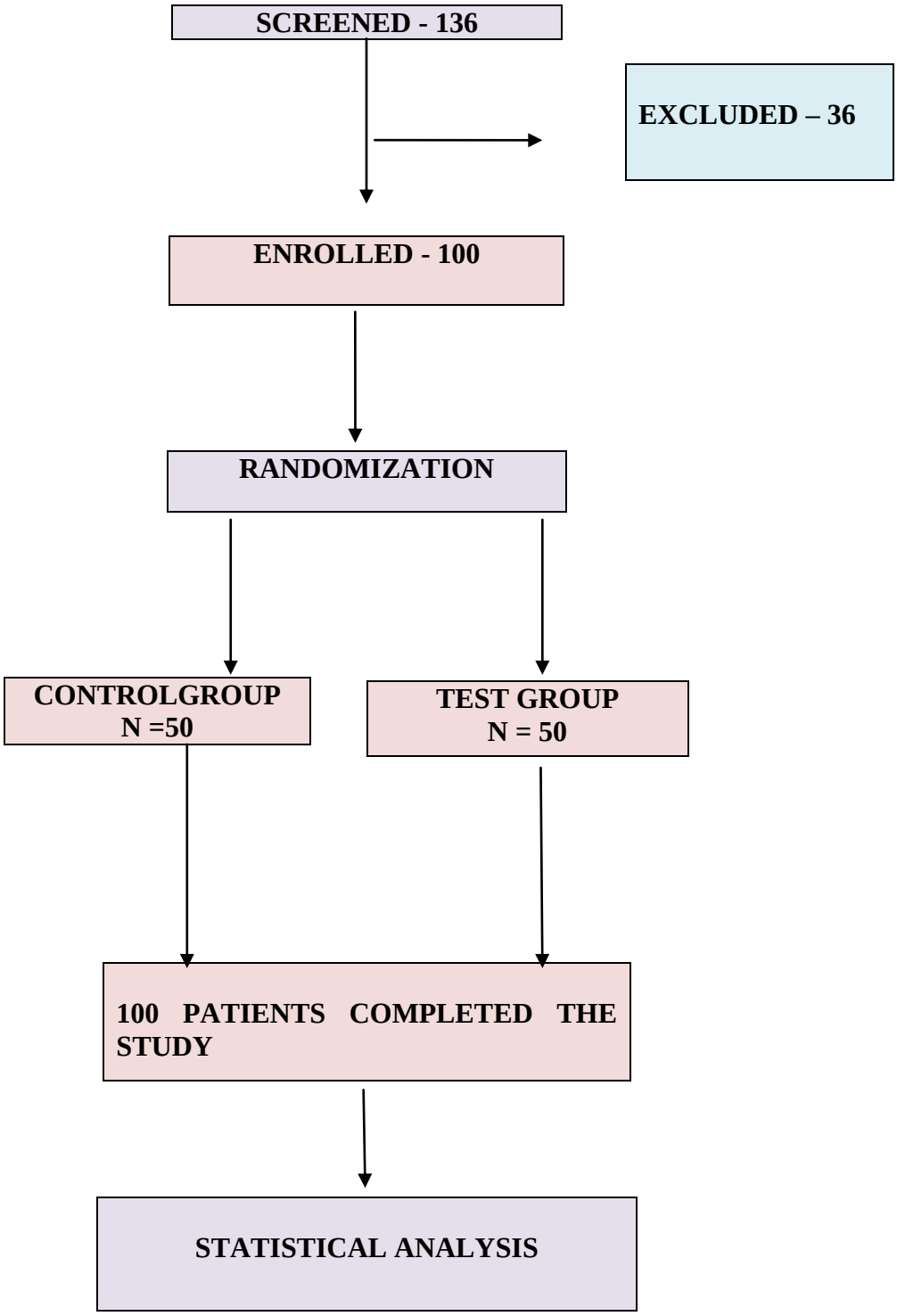
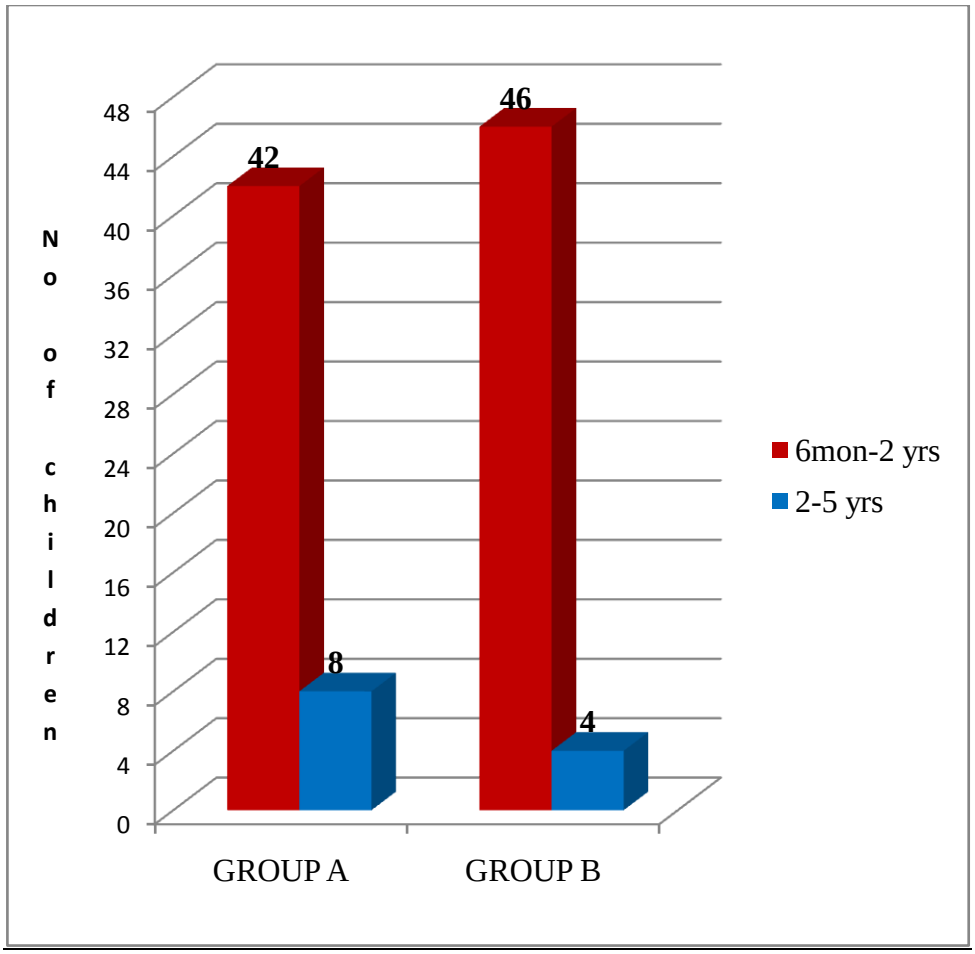

SCREENED - 136
EXCLUDED – 36
ENROLLED - 100
RANDOMIZATION
CONTROLGROUP
N =50
TEST GROUP
N = 50
100 PATIENTS COMPLETED THE STUDY
STATISTICAL ANALYSIS

Table –1 : AGE DISTRIBUTION

AGE	GROUP A		GROUP B	
	NO	PERCENTAGE	NO	PERCENTAGE
6months- 2 years	42	84%	46	92%
2-5 years	8	16%	4	8%

- Table 1 shows the age distribution of both the groups.
- 42 (84%) children in group A and 46(92%) in Group B were in the age group of 6 months to 2 years
- 8 (16%) children in group A and 4(8%) in Group B were in the age group of 2 to 5 years

FIGURE 1: AGE DISTRIBUTION



- Figure 1 depicts age distribution in both the groups.

TABLE 2: MEAN AGE DISTRIBUTION

GROUPS	(No of patients)	MEAN AGE (in months)	SD	p VALUE
GROUP A	50	16	15.8	0.278
GROUP B	50	17	15.8	

Table -2 shows the Age distribution of patients among both the groups

- The mean age of patients in Group A is 16 months and Group B is 17 months.
- There is no statistically significant difference in age between Group A and Group B.

FIGURE 2: MEAN AGE DISTRIBUTION

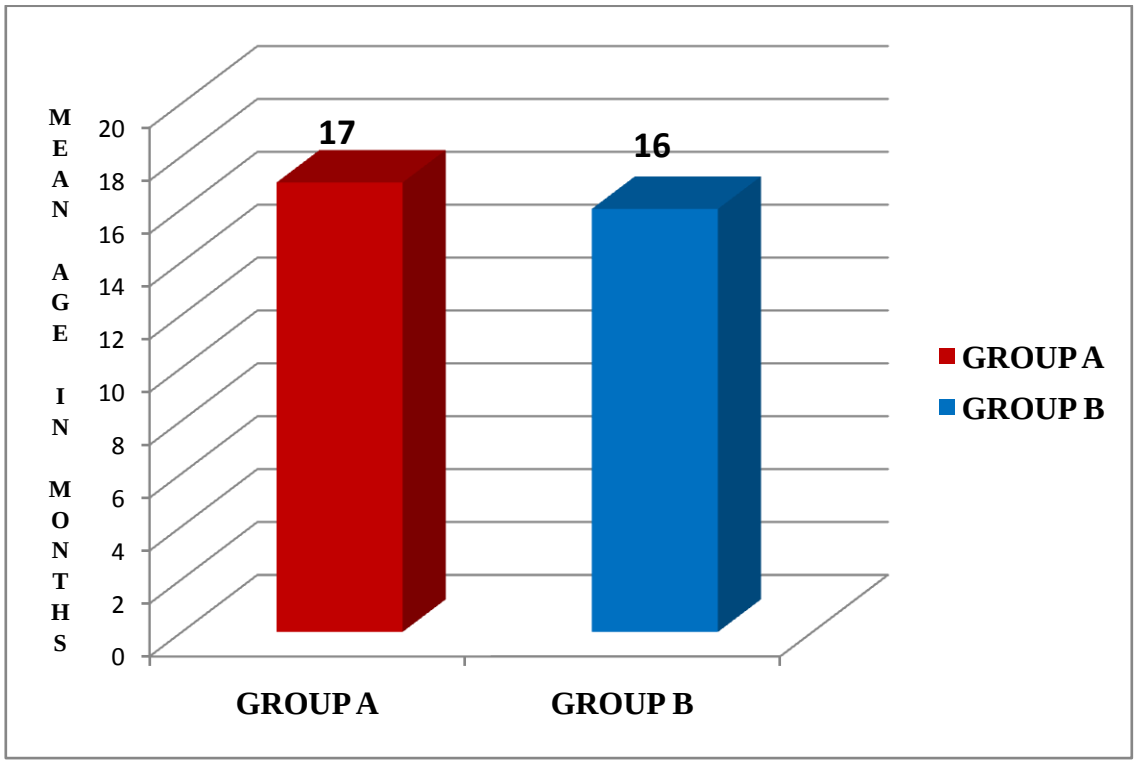


Fig 2 shows the distribution of age in Group A and Group B

Table -3: GENDER DISTRIBUTION

SEX DISTRIBUTION	GROUPS			
	GROUP A		GROUP B	
	n	%	n	%
MALE	31	62%	32	64%
FEMALE	19	38%	18	36%
TOTAL NO. OF PATIENTS	50		50	

Table -3 shows the distribution of male and female patients of two groups

- In Group A, 31(62%) patients were male and 19 (38%) patients were female.
- In Group B, 32(64%) patients were male and 18(36%) patients were female.

Fig -3: GENDER DISTRIBUTION

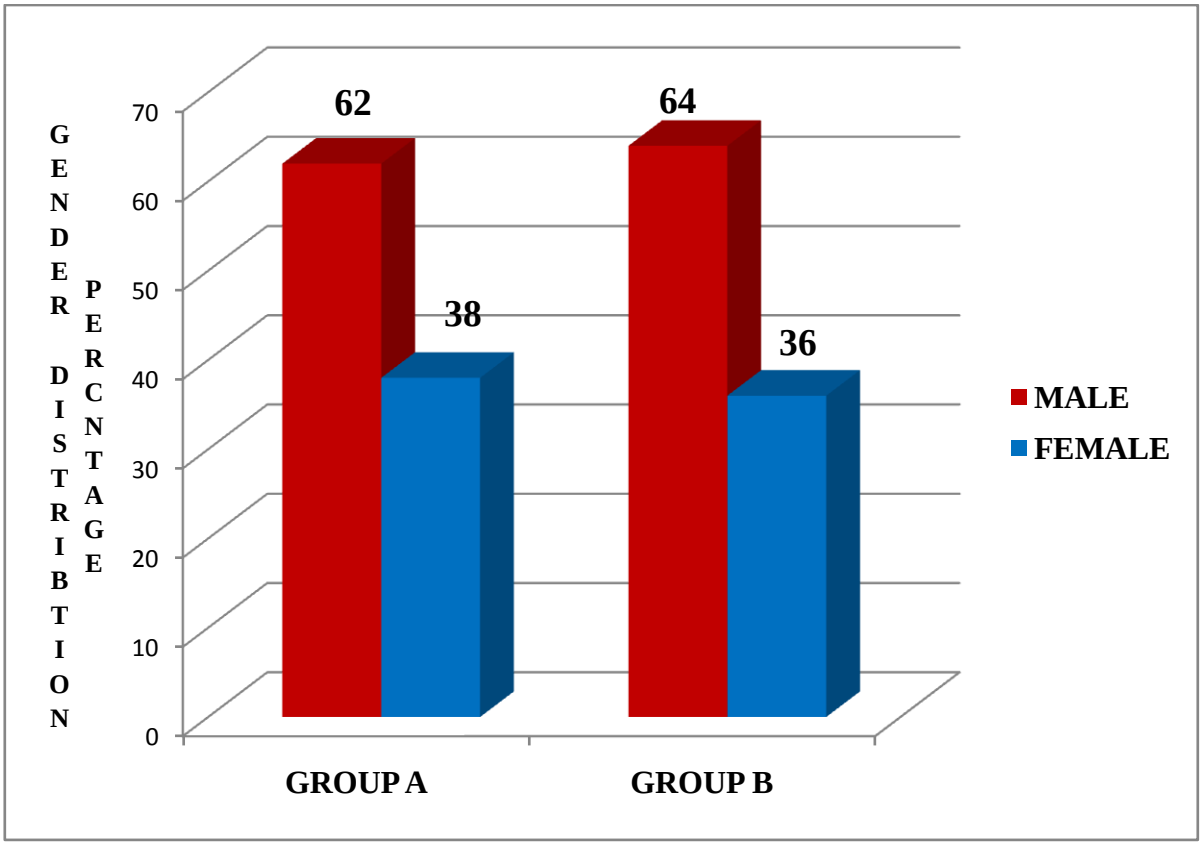


Fig 3 is the graphical representation of Table 3

Table 4: FREQUENCY OF DIARRHOEA

GROUPS	DAY 1		DAY 3		p value
	MEAN	SD	MEAN	SD	
GROUP A	9.03	3.41	0.81	1.01	<0.0001
GROUP B	10.1	4.42	6.24	3.32	0.006
p value	0.42		0.02		

Table – 4 shows the mean frequency of diarrhoea

- On comparing within the groups, there was a statistically significant reduction in the frequency of diarrhoea on day 3.
- On comparing between the groups, there was no statistically significant difference at baseline.

  There was a statistically significant difference between the groups on day 3 ($p < 0.02$).

Fig –4 : FREQUENCY OF DIARRHOEA

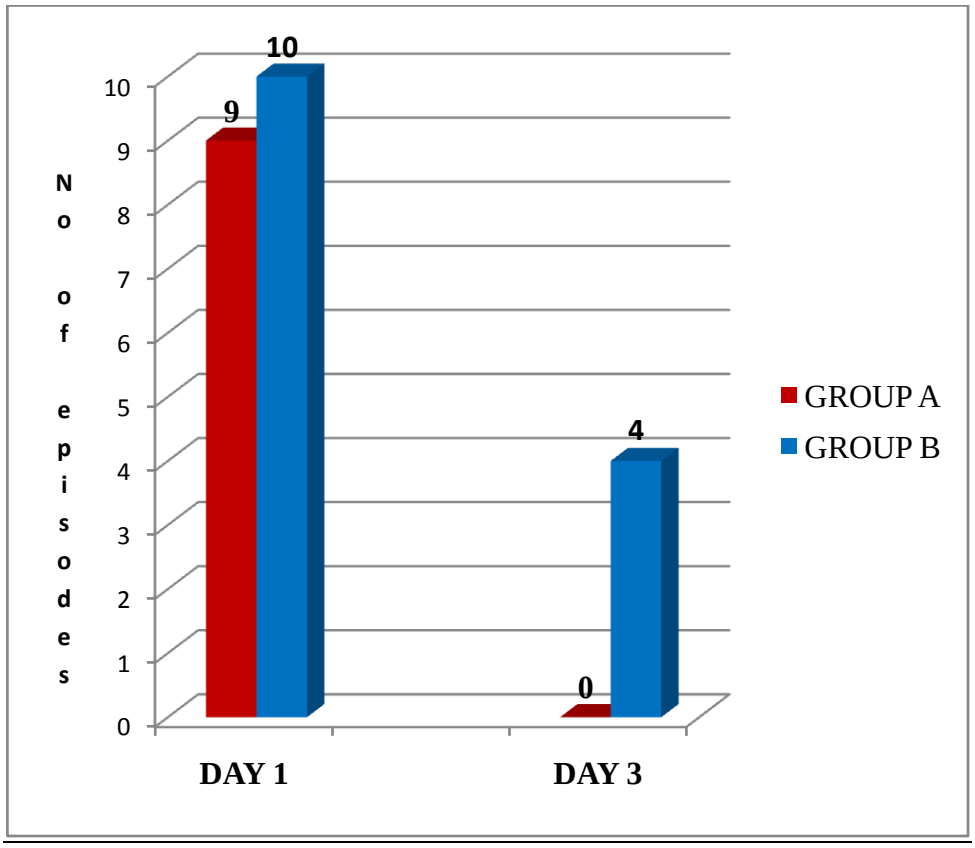


Fig 4 shows graphical representation of frequency of diarrhoea among Group A and B

Table -5: DURATION OF DIARRHOEA

GROUPS	Duration in hours	
	MEAN	SD
GROUP A	36.2	12.3
GROUP B	72.6	31.2
p value	0.001	

Table – 5 shows the mean duration of diarrhoea among group A and B

On comparing the two groups,

There was a statistically significant reduction in the duration of diarrhoea ($p<0.001$).

Fig –5 : DURATION OF DIARRHOEA

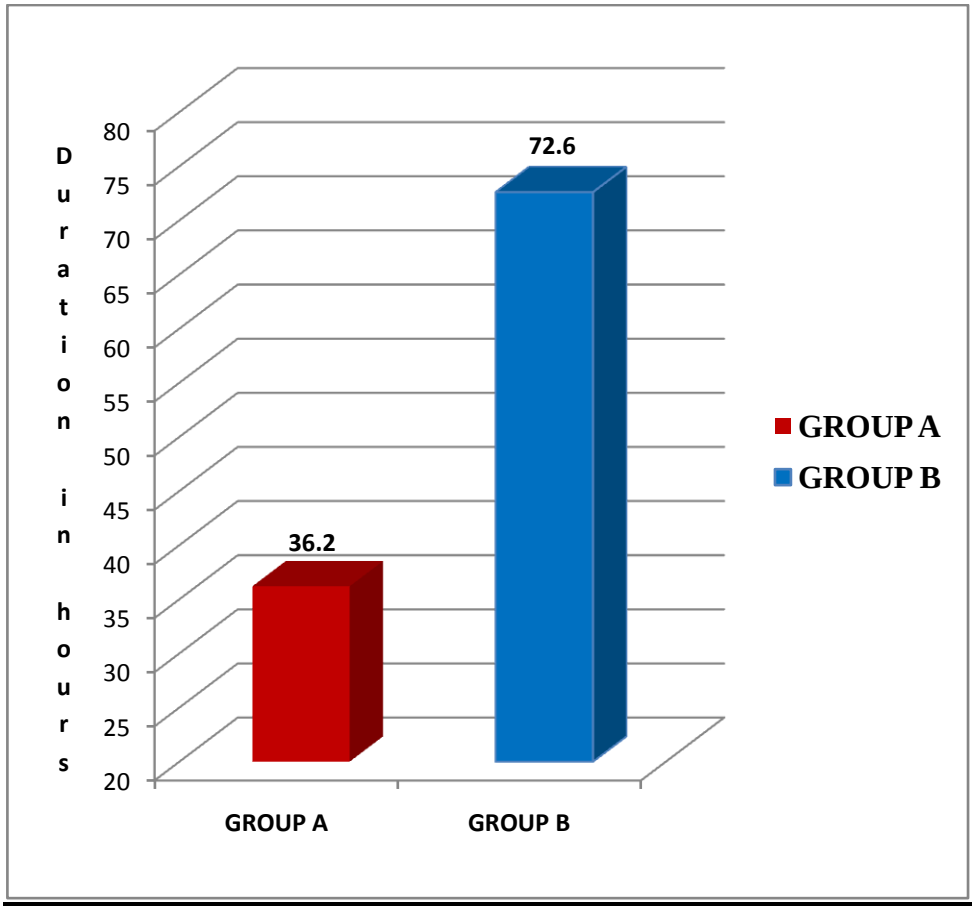


Fig 5 shows graphical representation of duration of diarrhoea among Group A and B.

Table 6: HYDRATION STATUS

NO. OF CHILDREN	GROUPS			
	GROUP A		GROUP B	
	n	%	n	%
WITH SOME DEHYDRATION	21	42%	24	48%
WITHOUT DEHYDRATION	29	58%	26	52%
TOTAL NO. OF CHILDREN	50		50	

Table 6 shows the hydration status of children in both groups

On comparing the two groups,

- In Group A, 21 (42%) children had some dehydration and 29 (58%) had no dehydration.
- In Group B, 24(48%) children had some dehydration and 26 (52%) had no dehydration
- None of the children had dehydration on day 3 in both the groups

Fig –6: HYDRATION STATUS

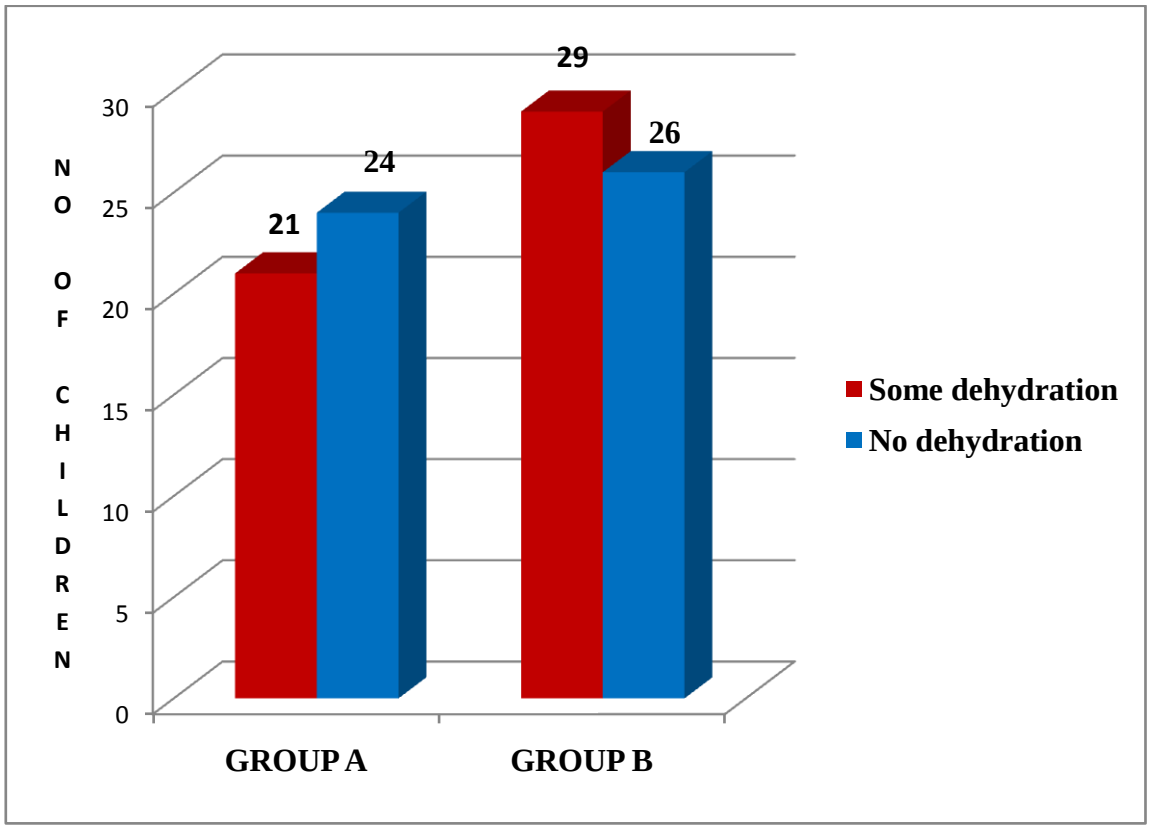


Fig 6 shows graphical representation of hydration status among Group A and B

Table 7: HEMATOLOGICAL PARAMETERS

PARAMETER	GROUP A			GROUP B		
	Day 1	Day 16	p VALUE	Day 1	Day 16	pVALUE
RBC COUNT Cells/cumm	3.5 million	3.6 million	0.43	3.6 million	3.5 million	0.45
TOTAL COUNT Cells/cumm	11557	11465	0.79	12043	11876	0.87
HAEMOGLOBIN In g/dl	11	11	0.55	11.5	11.5	0.71
PLATELET COUNT Cells/cumm	360000	350000	0.37	360000	370000	0.47

Table7 shows the haematological and biochemical parameters on Day 1 and at Day 16 in Groups A and B. The differences in lab parameters were not statistically significant in both the groups.

Table 8: RENAL FUNCTION TEST

PARAMETER	GROUP A			GROUP B		
	Day 1	Day 16	p VALUE	Day 1	Day 16	P VALUE
BLOOD SUGAR mg/dl	105	110	0.9	106	109	0.21
BLOOD UREA mg/dl	21	21	0.65	22	22	0.79
SERUM CREATININE mg/dl	1	1	0.52	1	1	0.55
SERUM SODIUM mEq/L	137	138	0.32	138	137	0.36
SERUM POTASSIUM mEq/L	4	4.2	0.36	4.1	4.3	0.33

Table 8 shows the results of renal function test on Day 1 and at Day 16 in Groups A and B. The differences in lab parameters were not statistically significant in both the groups.

Table 9: LIVER FUNCTION TEST

PARAMETER	GROUP A			GROUP B		
	Day 1	Day 16	p VALUE	Day 1	Day 16	p VALUE
SGOT IU/L	34	36	0.33	35	34	0.45
SGPT IU/L	43	43	0.68	45	46	0.78
BILIRUBIN mg/dl	1.1	1.1	0.97	1.1	1.1	0.92

Table 9 shows the results of liver function test on Day 1 and at Day 16 in Groups A and B. The differences in lab parameters were not statistically significant in both the groups.

Fig 7: RBC COUNT

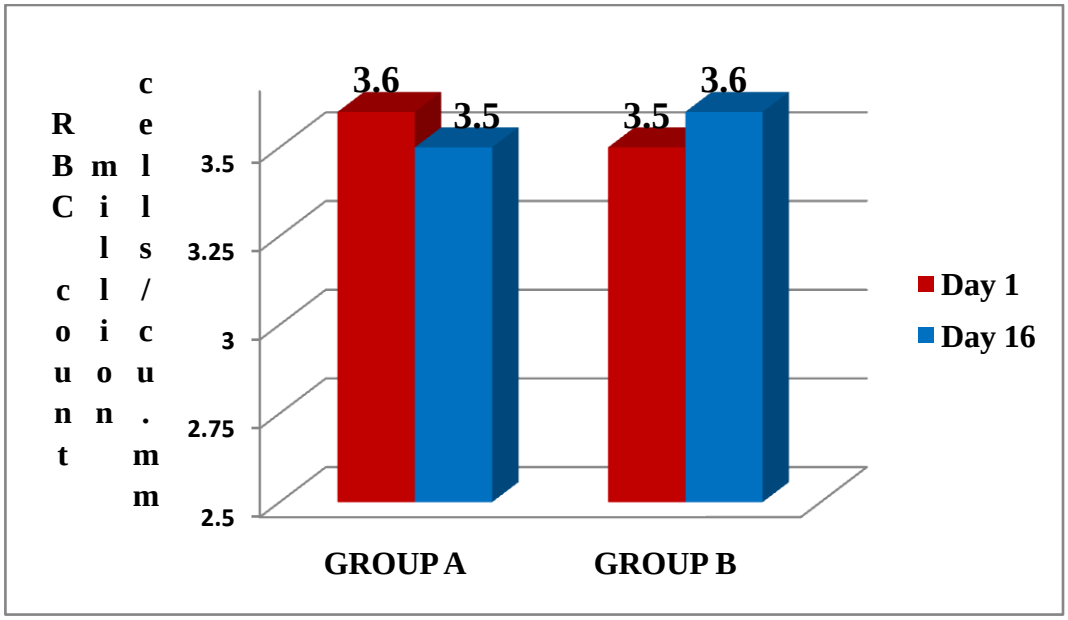


Fig 7 shows the difference in RBC count in a graphical way.

Fig 8: HAEMOGLOBIN

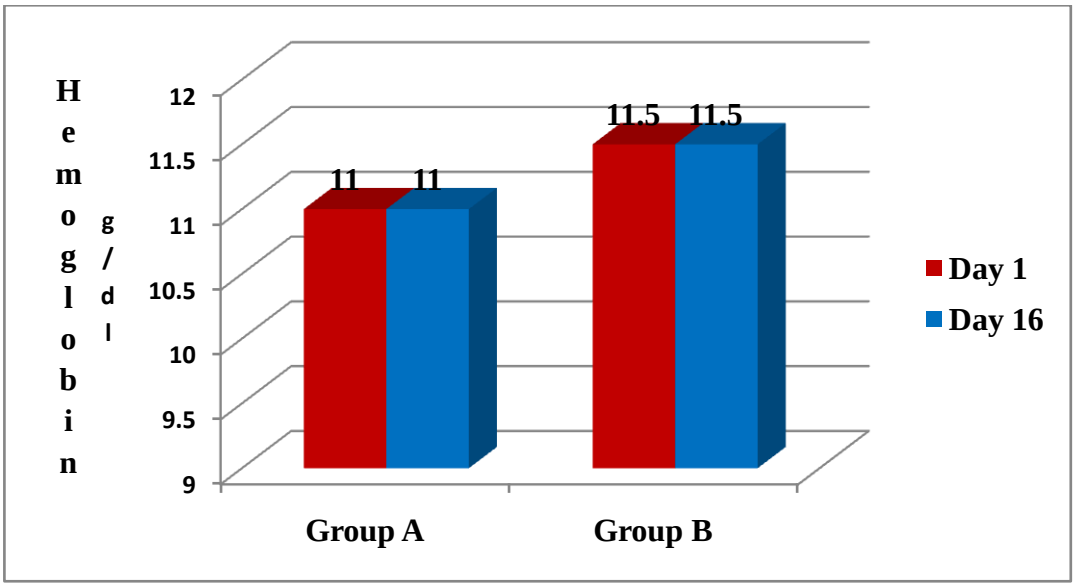


Fig 8 shows the difference in haemoglobin between Group A and B

Fig 9: TOTAL COUNT

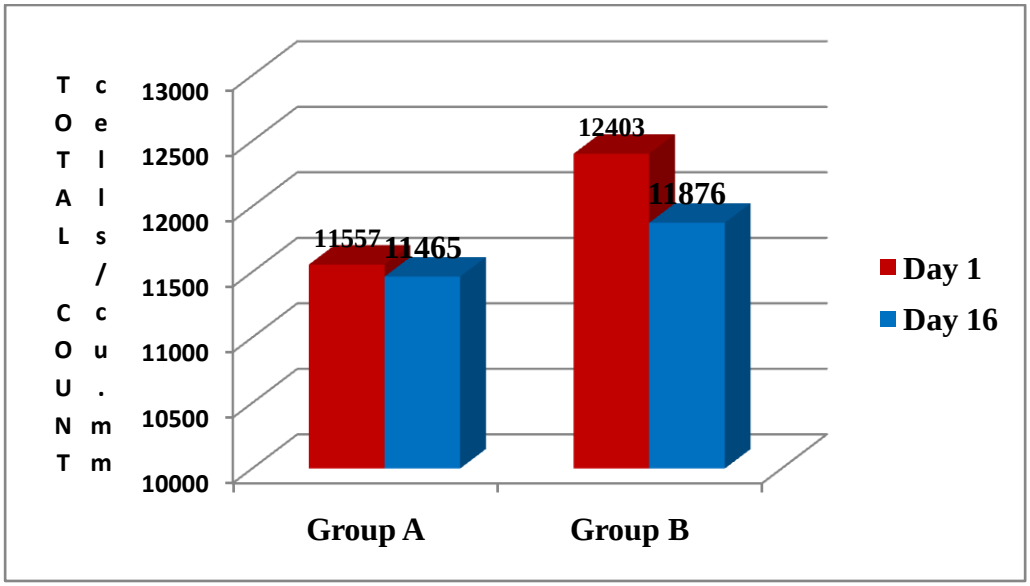


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Fig 9 shows the difference in Total count in a graphical way.

Fig 10: PLATELET COUNT

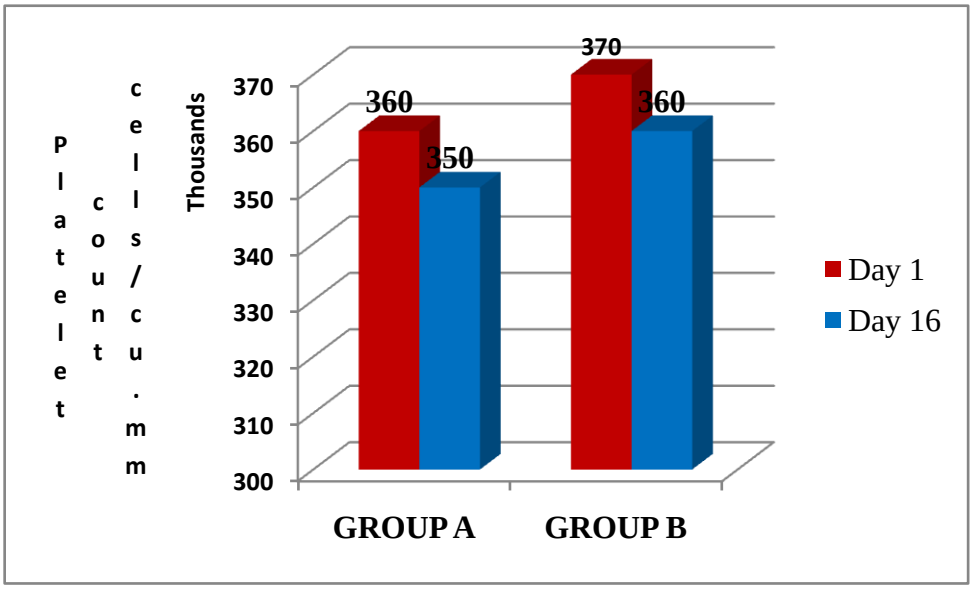


Fig 10 shows the difference in Platelet count in a graphical way.

Fig 11: BLOOD SUGAR

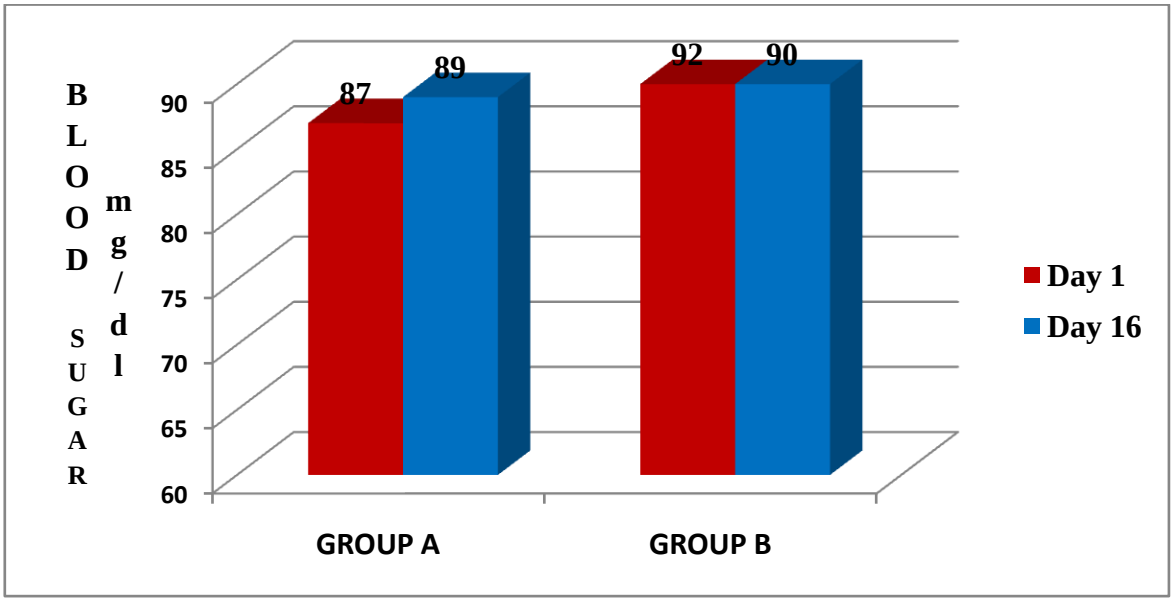
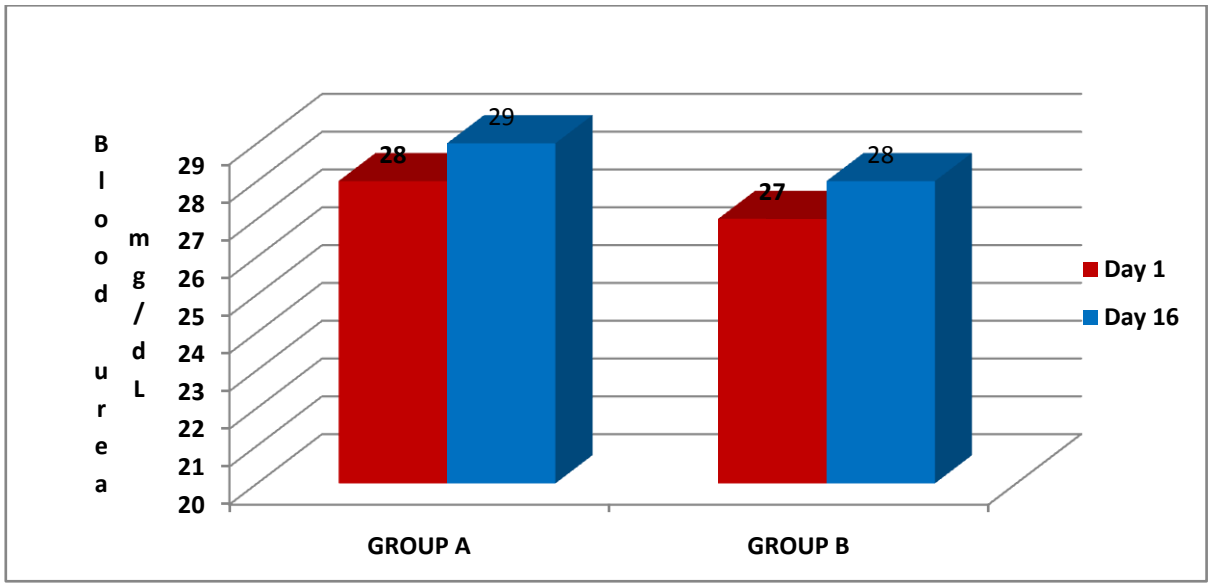


Fig 11 is the diagrammatic representation of mean blood sugar values in both groups

Fig 12 :BLOOD UREA



The mean blood urea levels in both groups is represented in Fig 12

Fig 13 :SERUM CREATININE

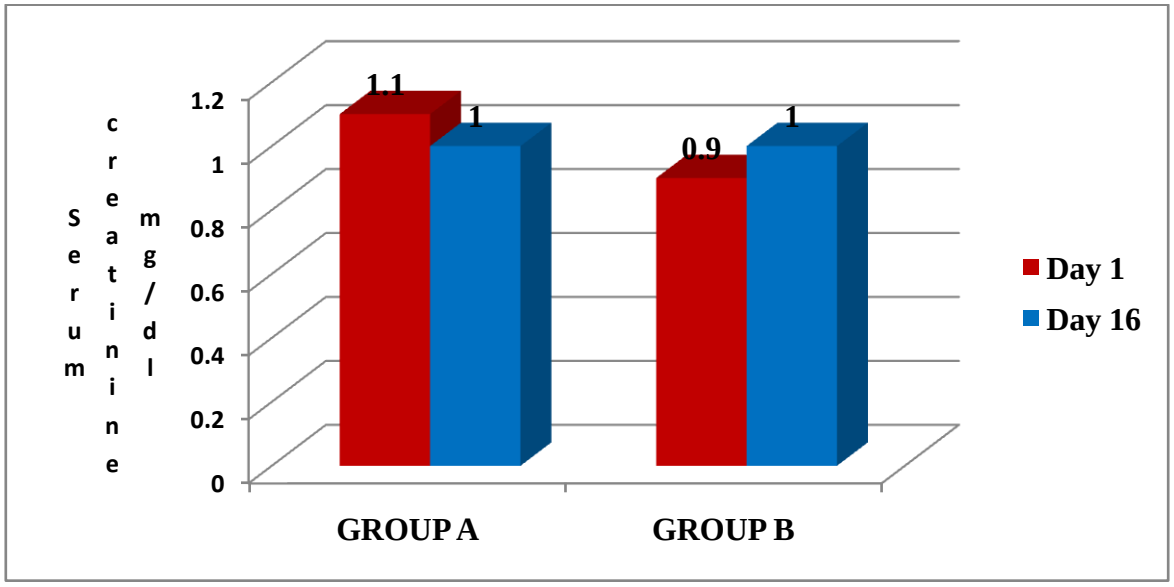
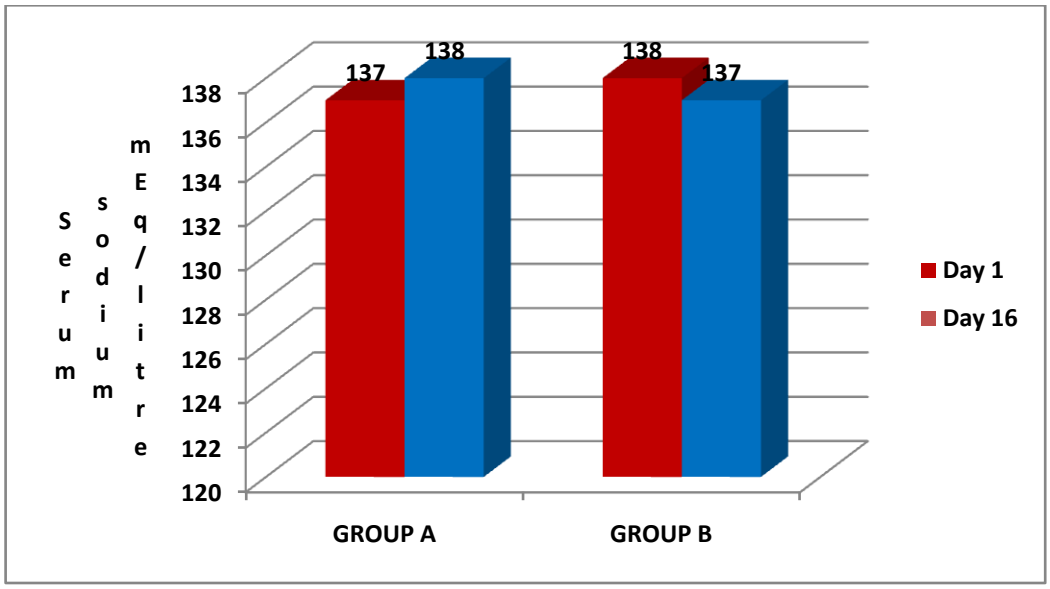


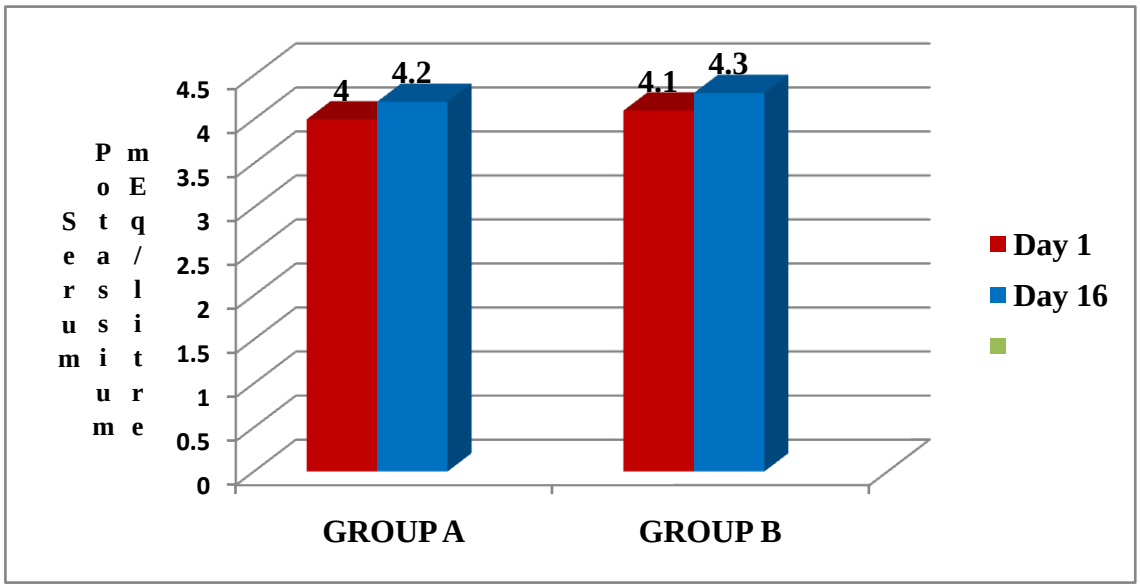
Fig 13 is the graphical representation of mean serum creatinine values in both groups before and at the end of treatment

Fig 14: SERUM SODIUM



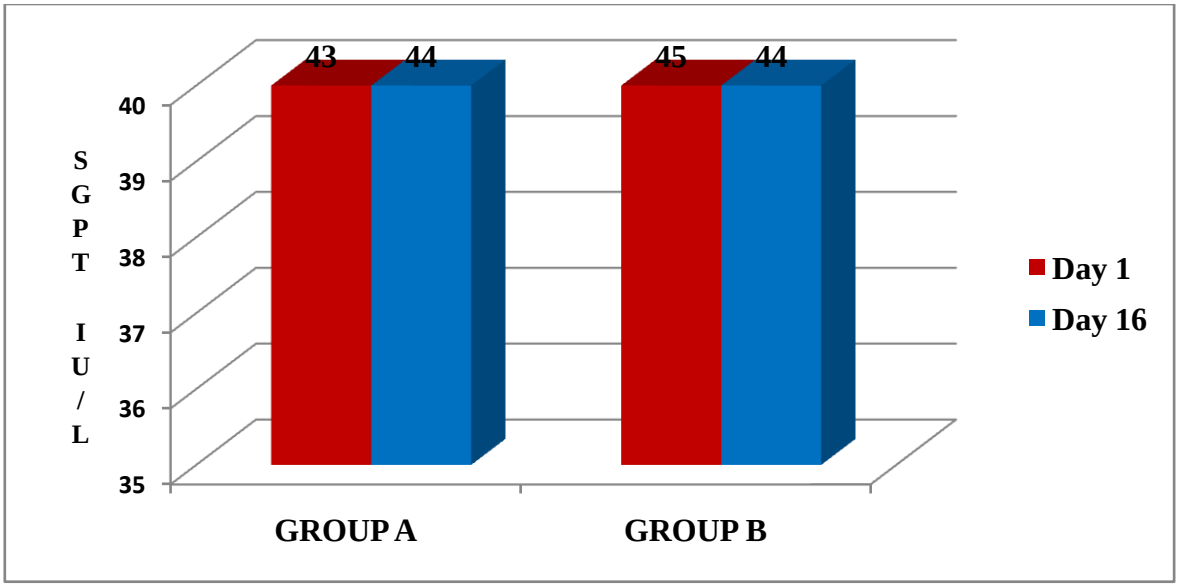
The mean serum sodium levels in both groups is represented in Fig 14

Fig 15 :SERUM POTASSIUM



The mean serum potassium levels in both groups is represented in Fig 15.

Fig 16: SGPT



The mean SGPT values in both groups is represented in Fig 16

Fig 17: SGOT

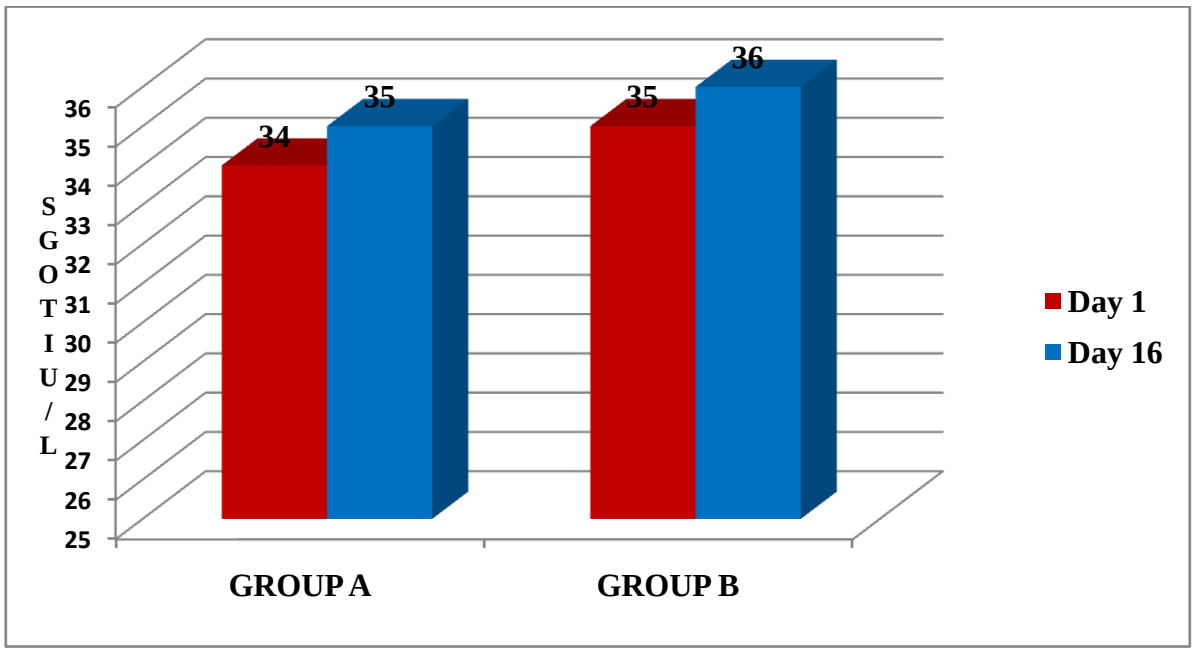


Fig 17 shows the mean SGOT values in Group A and B

TABLE 10: ADVERSE EVENTS

ADVERSE EVENTS	GROUP A	GROUP B
VOMITING	5	5
RASH	0	1
FATIGUE	8	7
ABDOMINAL PAIN	6	5

Table 10 shows the Adverse events reported in both groups. The adverse events were mild and no serious adverse effects were reported. There were no drop outs due to adverse events. Among the adverse events, it was found that fatigue was the most common followed by abdominal pain, vomiting and rash.

Fig 18: Adverse events

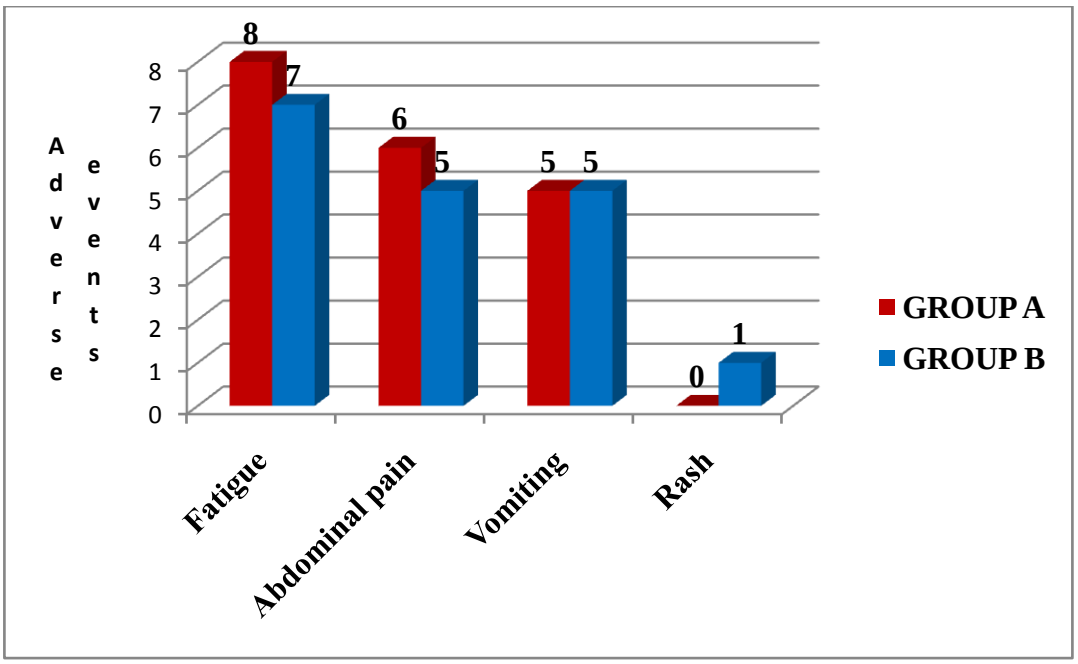


Fig 18 shows number of Adverse events in both groups

TABLE 11: INCIDENCE OF ADRs

	GROUP A	GROUP B
NUMBER OF ADRs	19	18

- Table 11 shows the incidence of ADRs presented by the patients in both the groups.
- In Group A, 19 ADRs were reported and in Group B, 18 ADRs were reported.

FIGURE 19: INCIDENCE OF ADRs

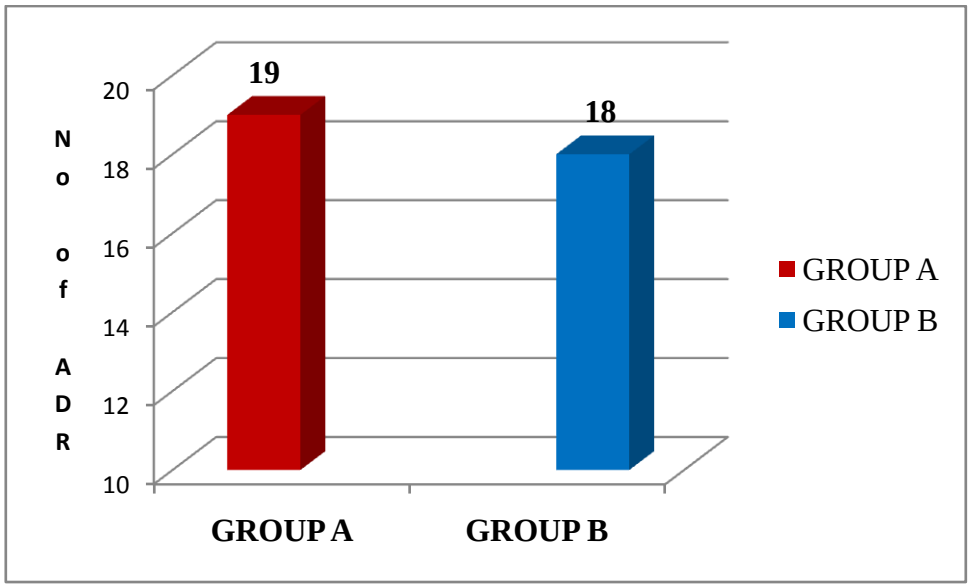


Figure 19 shows the graphical representation of incidence of ADRs.

TABLE 12 : CAUSALITY ASSESSMENT OF INDIVIDUAL ADR IN GROUP A

ADRs	Certain	Probable	Possible	Un-likely	Un-classified	Un-classifiable	Total
Fatigue	**-**	**-**	**8**	**-**	**-**	**-**	**8**
Abdominal pain	**-**	**-**	**6**	**-**	**-**	**-**	**6**
Vomiting	**-**	**-**	**5**	**-**	**-**	**-**	**5**
Rash	**-**	**-**	**0**	**-**	**-**	**-**	**0**
Total			**19**				**19**

- Table 12 shows causality assessment of individual ADR in Group A.
- Causality assessment was done using WHO causality assessment scale
- All adverse drug reactions were categorized as possible.

TABLE 13 : CAUSALITY ASSESSMENT OF INDIVIDUAL ADR IN GROUP B

ADRs	Certain	Probable	Possible	Un-likely	Un-classified	Un-classifiable	Total
Fatigue	-	-	**7**	-	-	-	**7**
Abdominal pain	-	-	**5**	-	-	-	**5**
Vomiting	-	-	**5**	-	-	-	**5**
Rash	-	-	**1**	-	-	-	**1**
Total			**18**				**18**

- Table 13 shows causality assessment of individual ADR in Group B.
- All ADRs were categorized as possible under WHO causality assessment scale.

TABLE 14: SEVERITY ASSESSMENT OF ADR

SEVERITY	GROUP A	GROUP B
MILD	19	18
MODERATE	--	--
SEVERE	--	--

- Table 14 shows severity assessment of Adverse Drug Reactions.
- Severity assessment was done using Modified Hartwig and Siegel scale.
- All the Adverse Drug Reactions in both the groups were mild.

DISCUSSION

Diarrhoea is a change in the individual bowel habit resulting in more frequent and/or loose stools. Diarrhoea can be considered as acute or chronic disease.

Acute diarrhoea is a self-limiting process. The most common age is between 6–24 months and when untreated diarrhoea can lead to dehydration, acidosis, and electrolyte imbalance.

The only treatment necessary is replacing fluid loss and electrolytes to correct dehydration. Fluid replacement is done by administration of oral rehydration solution and intravenous fluids if necessary. Synbiotic and Probiotic may help in reducing the frequency and duration of the diarrhoea.

The study was conducted to assess the safety and efficacy of synbiotic and probiotic in acute diarrhoea in children. 100 children were randomized into two groups and received either synbiotic or probiotic along with standard therapy.

The enrolled subjects were assessed on day 3 and day 8 by clinical examination. Lab investigations were done on day 1 and day 16. Data were compiled and results analyzed statistically.

There was no significant difference in the mean age of children in both groups in this study. This shows that the age distribution was similar in both the groups. Males were more in number than females in both the groups. This was similar to the study conducted by Huang JS et al[50] where males were more in number.

In this study there was a statistically significant reduction in the frequency of diarrhoea within the groups. This shows that both therapies were effective in reducing the frequency of diarrhoea. On comparing synbiotic with probiotics on day 3, there was a statistically significant reduction in the frequency of diarrhoea($p< 0.02$). This may probably be due to the effect of synbiotic in reducing the frequency of diarrhoea.

There was a statistically significant reduction in the duration of diarrhoea on comparing synbiotics with probiotics ($p<0.001$). This shows that the reduction in duration of diarrhoea may be due to the effect of synbiotic. This is in correlation with the studies conducted by Allen SJ (2004) , Dhingra U, Malik (2006) and Szajewska (2007) which also showed similar reduction of frequency and duration by adding synbiotics.[51,52,53]

There was no statistically significant difference in hematological parameters (RBC count, Total count , Differential count, Hemoglobin , Platelet count), renal function test (Blood Sugar, Blood Urea and Serum creatinine , Serum electrolytes) and Liver function test (Serum SGOT ,Serum SGPT) within the groups. This shows that Synbiotic and Probiotic did not have any effect on the haematological and biochemical lab parameters. This is similar to the results of study done by Robert John Boyle et al,[54] which also showed that Synbiotic did not affect haematological and biochemical lab parameters.

No serious adverse effects were reported in this study. All the Adverse Drug Reactions recorded were categorized as possible under WHO causality assessment scale. According to the Modified Hartwig and Siegel severity assessment scale all the adverse reactions reported were mild. There was no significant difference in the occurrence of adverse effects between the two groups suggesting that addition of synbiotics and

probiotics is not associated with increase in the incidence of adverse reactions. This was in correlation with the studies conducted by Boyle et al[54] and Basu et al[55] where addition of Synbiotics did not increase the frequency or severity of Adverse Drug Reactions.

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CONCLUSION

From this study we conclude that

- Synbiotic is effective in reducing the frequency of diarrhoea.
- Synbiotic is effective in reducing the duration of diarrhoea
- Synbiotic is well tolerated.

When administered along with standard therapy in children with acute diarrhoea, the possible mechanism being maintenance of intestinal barrier function and stimulation of host immunity.

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APPENDICES

APPENDIX-I

LIST OF ABBREVIATIONS USED

ADR – Adverse Drug Reaction

HLA – Human Leukocyte Antigen

ORS _ Oral rehydration solution

ORT _ Oral rehydration Therapy

i.v – Intravenous

EHEC – Enterohemorrhagic

AAD _ Antibiotic Associated diarrhoea

IBS – Irritable Bowel syndrome

IBD – Inflammatory Bowel disease

APPENDIX -II

CASE REPORT FORM

A randomized, open label, comparative study of Multi-strained synbiotic against single strained probiotic in children with acute diarrhoea

NAME :

AGE/SEX :

WEIGHT :

PLACE :

OP NO :

DIAGNOSIS :

VISIT 1

1 .Vitals:

2. Medical History:

3. General /systemic examination:

4. Investigations:

Complete blood count :

Serum electrolytes :

Blood urea:

Serum Creatinine :

VISIT 2

1 .Vitals:

2. Medical History:

3. Investigations:

Complete blood count :

Serum electrolytes :

Blood urea:

Serum Creatinine :

4. Adverse Events:

APPENDIX-111

Information to Participants

Title: "A Randomized, Open label, Comparative study of multi-strained synbiotic against single strained probiotic in acute diarrhoea in children "

Principal Investigator:

Name of Participant:

This study is being conducted in the Diarrhoea OPD and ward,institute of Child Health, Chennai. You are invited to take part in this study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

Acute Gastroenteritis is one of the most and frequent disease in the childhood, considering the advances in treatment, Lactobacillus has being well described as a probiotic which reduces the number of days of hospitalization and also the severity. The overall goal of this study is to investigate whether the modulatory effects of multi strained synbiotics is more effective than single strained Probiotic, in the gastrointestinal tract in restoration of intestinal function.We want to test the efficacy and safety of treatment with Multi-strained synbiotic in this condition.

We have obtained permission from the Institutional Ethics Committee.

The study design

All patients in the study will be divided into 2 groups A & B. You will be assigned to either of the groups. Group A will receive standard treatment + multi-strained synbiotic & Group B will receive standard treatment + single strained probiotic.

Study Procedures

The study involves evaluation of safety and efficacy of synbiotic against probiotic. The planned scheduled visits involve visits at 1st and 7th day of the week . You will be required to visit the hospital 2 times during the study.

At each visit, the study physician will examine you. Blood tests will be carried out once during the study and about 5 ml blood will be collected. These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you.

In addition, if you notice any adverse events, you have to report it. You will be required to return unused study medicines when you report for your scheduled visits. This will enable correct assessment of the study results.

Possible benefits to you – synbiotic along with standard treatment will provide faster recovery in your children

Possible benefits to other people - The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not loose any benefits to which you are entitled.

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator Signature of Parent/ Guardian

Date

APPENDIX-1111

INFORMED CONSENT FORM

A randomised open label, comparative study of Multi-strained synbiotic against single strained probiotic in children with acute diarrhoea.

Name of the Participant:

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent that my child be included as a participant in this study.

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I am aware of the fact that I can opt out my child of the study at any time without having to give any reasonand this will not affect my future treatment in this hospital.

6. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC.Iunderstand that they are publicly presented.

7. I have understand that my identity will be kept confidential if my data are publicly presented

8. I have had my questions answered to my satisfaction.

9. I have decided my child to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signingthis consent form I attest that the information given in this document has been clearly explained to meand understood by me, I will be given a copy of this consent document.

1.Name and signature / thumb impression of the Parent/ Guardian

Name _____ Signature_____ Date_____

2.Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____ Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____ Date_____

சுய ஒப்புதல் படிவம்

ஆராய்ச்சி தலைப்பு:

குழந்தைகளின் வயிற்றுபோக்கு சிகிச்சையில் சின்பயாடிக் மற்றும் ப்ரோபயாடிக்கின் திறன் ஒரு திறந்தநிலை ஒப்பிடுதல் ஆய்வு.

பெயர் : தேதி :

வயது : வெளி நோயாளி எண்:

பாலினம் : ஆராய்ச்சி சேர்க்கை எண்:

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்து கொண்டு நான் எனது சம்மதத்தைத் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின் பேரில் தான் என் குழந்தையை பங்கு பெற சம்மதிக்கிறேன் மற்றும் நான் இந்த ஆராய்ச்சியிலிருந்து எந்நேரமும் பின் வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

இந்த ஆராய்ச்சியின் விவரங்களைக் கொண்ட தகவல் தாளைப் பெற்றுக் கொண்டேன்.

இந்த ஆய்விற்காக என் குழந்தைக்கு இரத்தப் பரிசோதனை செய்துக் கொள்ள சம்மதிக்கிறேன்.

இந்த ஆய்வை முழு சுதந்திரத்துடன் மற்றும் சுயநினைவுடன் பங்கு கொள்ள சம்மதிக்கிறேன்.

கையொப்பம்.

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சி தலைப்பு:

குழந்தைகளின் வயிற்றுபோக்கு சிகிச்சையில் சின்பயாடிக் மற்றும் ப்ரோபயாடிக்கின் திறன் ஒரு திறந்தநிலை ஒப்பிடுதல் ஆய்வு.

இந்த ஆய்வு குழந்தைகள் நல சிறப்பு மருத்துவமனை மற்றும் ஆராய்ச்சி நிலையத்தில் நடைபெற உள்ளது.

நீங்கள் உங்கள் குழந்தையை இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆய்வில் உங்கள் குழந்தைகயின் வயிற்றுபோக்கு சிகிச்சைக்காக சின்பயாடிக் மற்றும் ப்ரோபயாடிக் ஒரு நாளைக்கு இருமுறை கொடுக்கப்படும். இருமுறை இரத்த பரிசோதனை செய்யப்படும். அதற்காக எடுக்கப்படும் இரத்தத்தின் அளவு அதிகபட்சம் 5மி.லி. மட்டுமே.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களது குழந்தையின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின் பேரில் தான் இருக்கிறது. மேலும் நீங்கள் எந்நேரமும் உங்கள் குழந்தையை இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு சிகிச்சையின் முடிவுகளை ஆராய்ச்சியின் போதோ அல்லது ஆராய்ச்சியின் முடிவின் போதோ தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

EC RegNo.ECR/270/Inst./TN/2013

Telephone No:044 25305301
Fax : 044 25363970
Date: 16.08.2013

CERTIFICATE OF APPROVAL

To
Dr.S.A.Ayisya,
II year MD Pharmacology,
Madras Medical College, Chennai-3,
Dear Dr.S.A.Ayisha,

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "A randomized open label comparative study of multi strained symbiotic against single strained probiotic in children with acute diarrhoea" No.13082013.

The following members of Ethics Committee were present in the meeting held on 13.08.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.G.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. Kalai Selvi -- Member
   Prof of Pharmacology, MMC, Ch-3
6. Prof. Siva Subramanian, -- Member
   Director, Instt. of Internal Medicine, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nadhini 26/8/13
Member Secretary, Ethics Committee

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003